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**Oral cancer of the retromolar area: A study of the
anatomy, pathology and natural history**

By

Anestis K Isaakidis

A thesis submitted in total

fulfilment of the requirements for the

degree of

Master of Science in Surgery

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University of Glasgow

Plastic Surgery Unit, Canniesburn Hospital

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Abstract

This thesis centres on cancer of the retromolar triangle (RMT), an uncommon head and neck cancer. The retromolar trigone area is the region within the oral cavity defined by the American Joint Committee on Cancer (AJCC) as the attached mucosa overlying the ascending ramus of the mandible from the level of the posterior surface of the last molar tooth to the apex superiorly, adjacent to the tuberosity of the maxilla. The main points of significance about this area are that diagnosis may be delayed, the region is less accessible, and reconstruction is somewhat more difficult. Review of the literature revealed that there is a paucity of information regarding factors affecting diagnosis, treatment and prognosis of RMT cancer. The aim of this study was to assess the anatomy of the RMT and the pathology and natural history of cancer in this area to evaluate the present strategies for treatment.

Gross cadaveric dissections were performed in the RMT on both sides of the oral cavity to examine the normal anatomy and to identify anatomical structures that could possibly be affected by excisional surgery. Structures liable to damage were the lingual nerve, the inferior alveolar nerve, the buccal nerve, the palatoglossus muscle, the medial pterygoid muscle, the insertion of the temporalis muscle and less frequently the submandibular duct. Damage to these structures could affect sensation, speech, swallowing and chewing.

The medical records of 113 patients with histologically proven squamous cell carcinoma of the RMT, treated at Canniesburn Hospital, Glasgow, between 1985 and 1999, were reviewed retrospectively in order to study the natural history of the disease. The male: female ratio was 2.2:1 and the average age was 65 years. A total of 9.7% of patients were clinically staged as T1, 41.6% were T2, 16% were T3 and 32.7% were T4. At presentation 71 patients (63%) had a clinically negative neck, while 85 patients (75%) had a neck dissection at the time of treatment of the primary. A comparison between the clinical and pathological T and N stages highlighted the difficulties of clinical TNM staging with upstaging of the primary T

stage in 15.5% of patients and downstaging in 11% and upstaging of neck disease in 21% and downstaging in 9%.

Despite advances in treatment, this series has shown no significant improvement in survival over the 15-year study period. The determinant 5-year survival rates by the Kaplan-Meier method were pT1: 75%, pT2: 40%, pT3: 47%, pT4: 32% and overall 42%. In total 34% of patients died of disease directly related to their retromolar trigone cancer and this included 12% with systemic failure. Loco-regional failure of the retromolar trigone cancer accounted for death in 21%.

The understanding of the retromolar trigone tumours as a separate entity from other intraoral squamous cell carcinomas should allow us to formulate different strategies for its treatment in the future.

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Ancstis Isaakidis

DECLARATION

I, Anestis Isaakidis, certify that this Thesis entitled “Oral cancer of the retromolar area: A study of the anatomy, pathology and natural history” is result of my own research, that it does not incorporate without due acknowledgement any material submitted for a degree or diploma in any university.

I also affirm that it does not contain any materials previously published, written or produced by any other person (including information from the World Wide Web and the Internet) except where due reference is made in the text.

«Εν οίδα ότι ουδέν οίδα»
Σωκράτης

"The only true wisdom is in knowing you know nothing"
Socrates

Introduction

Retromolar trigone (RMT) cancer is an uncommon head and neck cancer. The retromolar trigone area is the region within the oral cavity overlying the ascending ramus of the mandible from the level of the posterior surface of the last molar tooth to the apex superiorly, adjacent to the tuberosity of the maxilla.

Due to the small size of the retromolar trigone, tumors arising here usually involve the adjacent anterior tonsillar pillar, tonsillar fossa, or soft palate. Distinguishing a single site of origin is often impossible. Diagnosis may be delayed since tumor may remain dormant for quite some time until the patient becomes symptomatic. In most cases, the primary presenting symptom is pain that is worsened by chewing. Other symptoms include referred otalgia and trismus.

Nearly all of these cancers are squamous cell carcinomas. In early disease (Stages I and II) surgery or radiation alone with elective neck treatment (secondary to the tendency for regional nodal spread) is most often utilized. For advanced stages, multimodality therapy with surgery and postoperative radiation is often used. Another point of significance about this area is that, the region is less accessible and surgical excision and reconstruction is somewhat more difficult.

A review of the medical literature was performed by using OVID/Medline and PubMed search strategies. Keywords entered included retromolar trigone, intraoral squamous cell carcinoma, natural history, recurrence, survival. Review of the literature revealed that there is a paucity of information regarding factors affecting diagnosis, treatment and prognosis of the RMT cancer. The aim of this study was to assess all these factors by looking into the anatomy of the area, the pathology of the cancer and the natural history of the disease. This would ultimately lead to an evaluation of the present strategies in treatment.

Literature review

Anatomy

The retromolar trigone is part of the oral cavity (Figure 1). The oral cavity is defined as the region that extends from the skin-vermilion junction of the lips to the junction of the hard and soft palate above and to the line of the circumvallate papillae below. The anterior tonsillar pillar or palatoglossal arch is the lateral border between the oral cavity and the oropharynx.

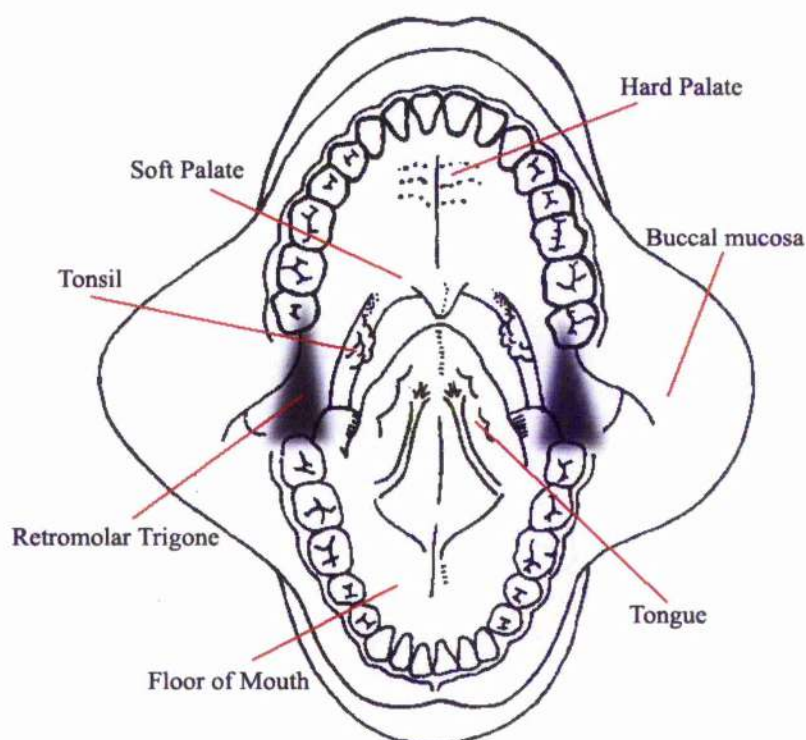


Figure 1 Anatomy of the oral cavity.

The retromolar trigone is a poorly defined area covered under the terms “posterior floor of the mouth,” “posterior alveolus,” and “anterior tonsillar pillar”. Bertelli in 1915 described the “area” as the “retromolar space”, being the portion joining the two alveolar borders, superior and inferior, as well as parts of these borders that lie behind the roots of the last molar teeth (1). Barbosa in 1959 used the term retromolar “area” rather than “region”, seeing that it lacks definite anatomical limits, as the part of the buccal cavity which lies between the

two dental arcades on either side and behind the roots of the last molar teeth, and which establishes a communication between the medial and vestibular portions of the buccal cavity when the dental arcades lie in contact (2).

The definition used mostly nowadays comes from the American Joint Committee on Cancer (AJCC): "Retromolar Gingiva (Retromolar Trigone or Pterygomandibular Raphe) (ICD-0 145.6). This is the attached mucosa overlying the ascending ramus of the mandible from the level of the posterior surface of the last molar tooth to the apex superiorly, adjacent to the tuberosity of the maxilla" (3).

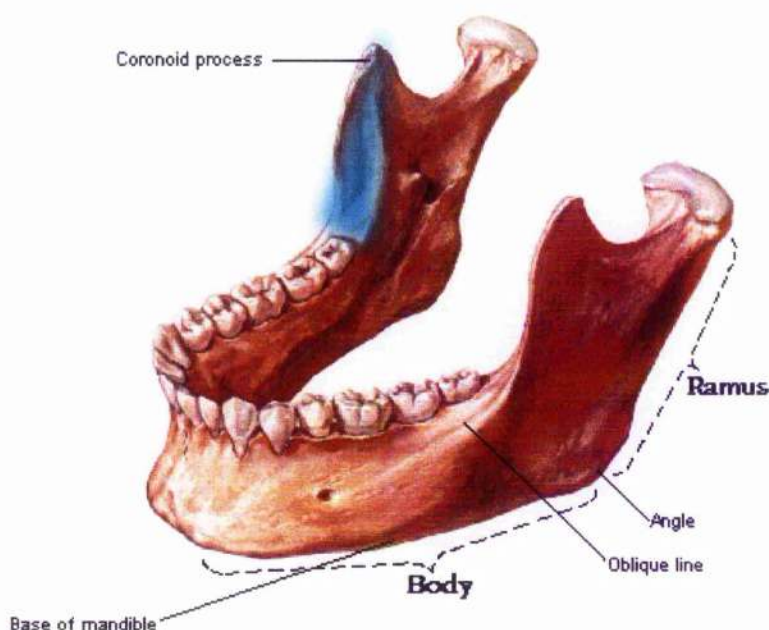


Figure 2 Retromolar Trigone (blue shadowed area) on the mandible. (From Netter FH: Interactive Atlas of Human Anatomy, Ciba-Geigy, 1995. Modified by the author)

The definition of the triangle is as following: the distal surface of the last lower molar tooth forms the *base*, the maxillary tuberosity forms the *apex*, the upward extension of the oblique line of the mandible to the coronoid process forms the triangle's *lateral side*, and a line connecting the distal lingual cusp of the last molar and the coronoid process forms the *medial side*. The triangle's base is continuous laterally with the gingivobuccal sulcus and

medially the gingivolingual sulcus. The triangle's lateral side is continuous with the buccal mucosa, and the medial side blends into the anterior tonsillar pillars (Figure 2 & Figure 3).

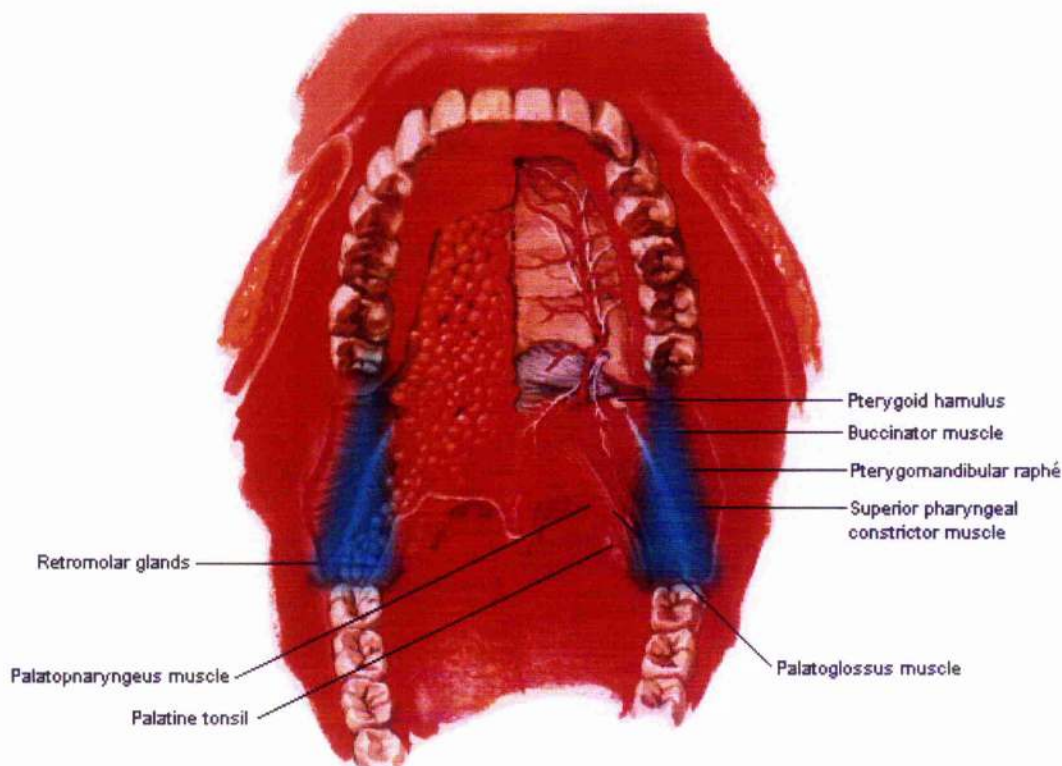


Figure 3 Anatomy of the retromolar trigone (blue shadowed area). (From Netter FH: Interactive Atlas of Human Anatomy, Ciba-Geigy, 1995. Modified by the author)

The mucosa of RMT as the rest of the oral cavity is lined by stratified squamous epithelium. The underlying submucosa contains minor salivary glands. The thickness of the mucosa over the RMT is considerably thicker (4.03 ± 1.15 mm on average) compared to the rest of the oral mucosa (0.5-1.5 mm range) (4;5). It is flaccid like the buccal mucosa, being greatly mobile and elastic at the angle joining the two alveolar arcades. It lies over the pterygomandibular raphe, which links the buccinator muscle and the superior constrictor of the pharynx. The buccopharyngeal fascia lies immediately below the buccinator muscle and the superior constrictor of the pharynx and separates them from the buccal pad of fat. By following this pad the deep structures of the RMT are visualized. Laterally lie the masseter

muscle and the anterior border of the ascending ramus, almost all of which is invested by the tendinous insertion of the temporalis muscle (Figure 4).

Horizontal Section - Superior View

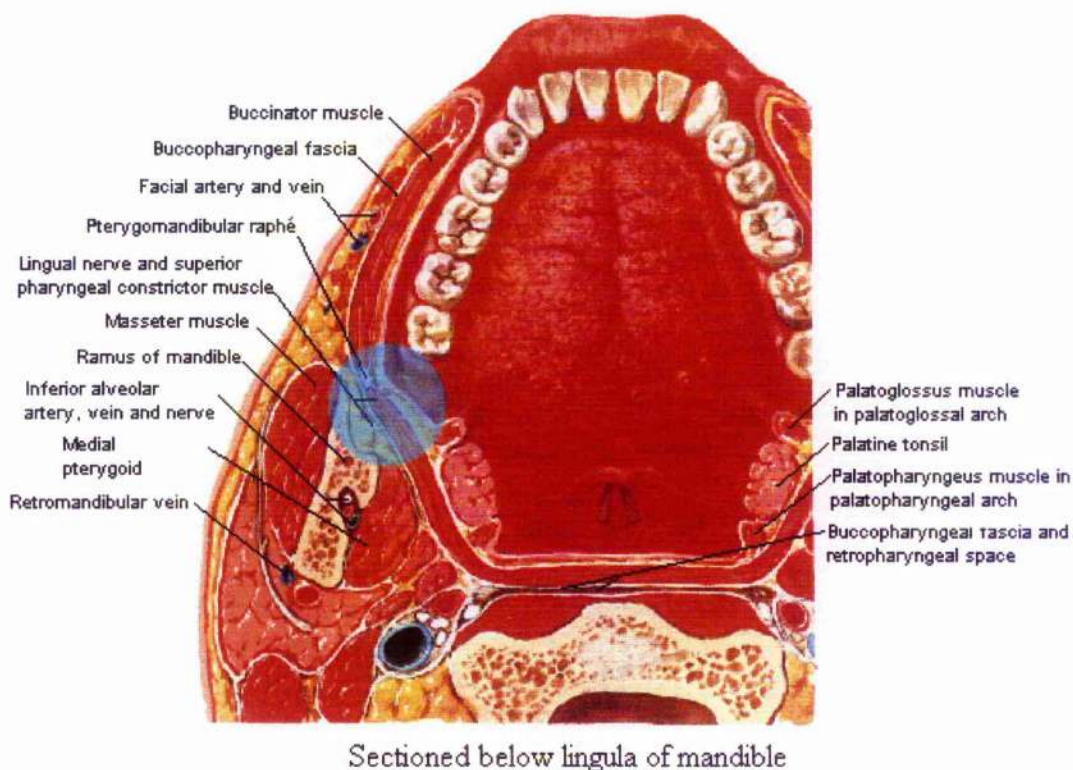


Figure 4 Horizontal section of the mouth (retromolar trigone: blue shadowed area). (From Netter FH: Interactive Atlas of Human Anatomy, Ciba-Geigy, 1995. Modified by the author)

Crossing this border is the buccal nerve. Medially lies the anterior edge of the medial pterygoid muscle. In the acute deep angle formed by the medial pterygoid and the ascending ramus, which is open superiorly, run the two branches of the mandibular nerve - the inferior alveolar and the lingual nerve (Figure 5). These three nerves – the buccal, inferior alveolar and lingual – are all sensory and easily accessible to cancerous infiltration from the retromolar area, explaining the painful symptomatology of these tumors (2). Furthermore, the anatomical variations of the position of the lingual nerve, which can be above the lingual

crest (14.5%) or even into the retromolar area (0.15%), makes it vulnerable to the usually required margins of tumour excision (6).

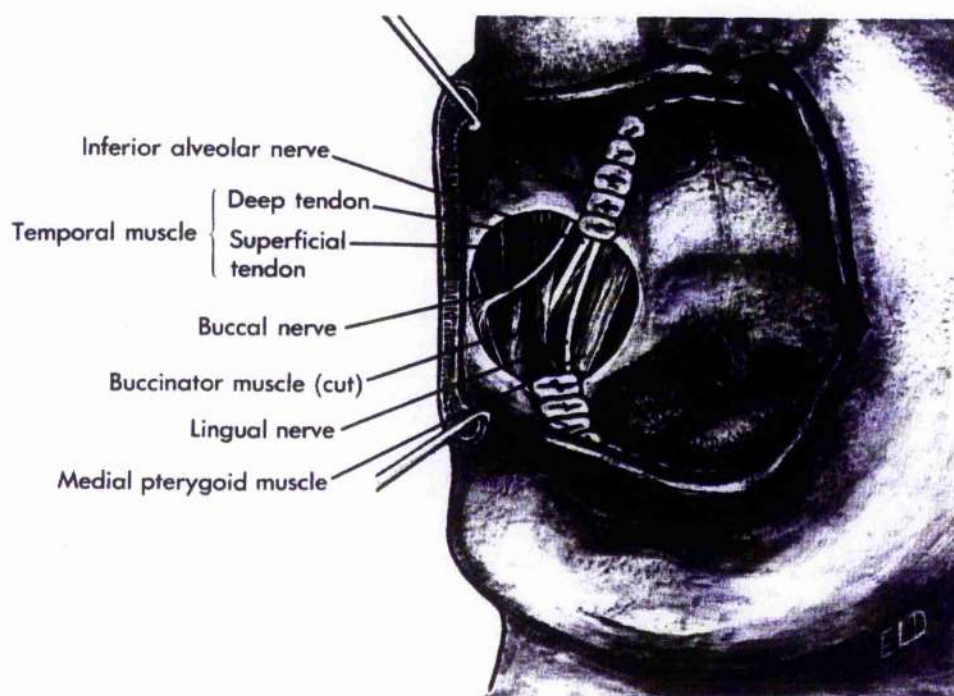


Figure 5 Vulnerable nerves at the retromolar trigone. (Modified from Sicher and Dubrul: Anatomy of Local Anesthesia. In: Oral anatomy)

The buccal pad of fat passes into the pterygomandibular angle, ascends to the zygomatic or infratemporal fossa, and occupies the free space between the pterygoid and temporalis muscles; it surfaces at the lower limit of the temporal fossa enclosing the anterior border of the temporalis muscle. It is along the weak fatty tissue of this pad of fat that the deeper layer of the area passes through the complicated planes of the zygomatic and pterygomaxillary fossae and to the inferior part of the temporal fossa. This fact explains the pattern of deep infiltration of retromolar tumors reaching and including the deep spaces of the tonsillar and prestyloid pharyngeal space, seeing that all these spaces intercommunicate amply(2).

The blood supply is from the tonsillar and ascending palatine branches of the facial artery, with contributions from the dorsal lingual, ascending pharyngeal, and lesser palatine arteries

(Figure 6). Venous drainage is through the tonsillar bed to the pharyngeal plexus of veins and to the common facial vein (7;8) (Figure 7).

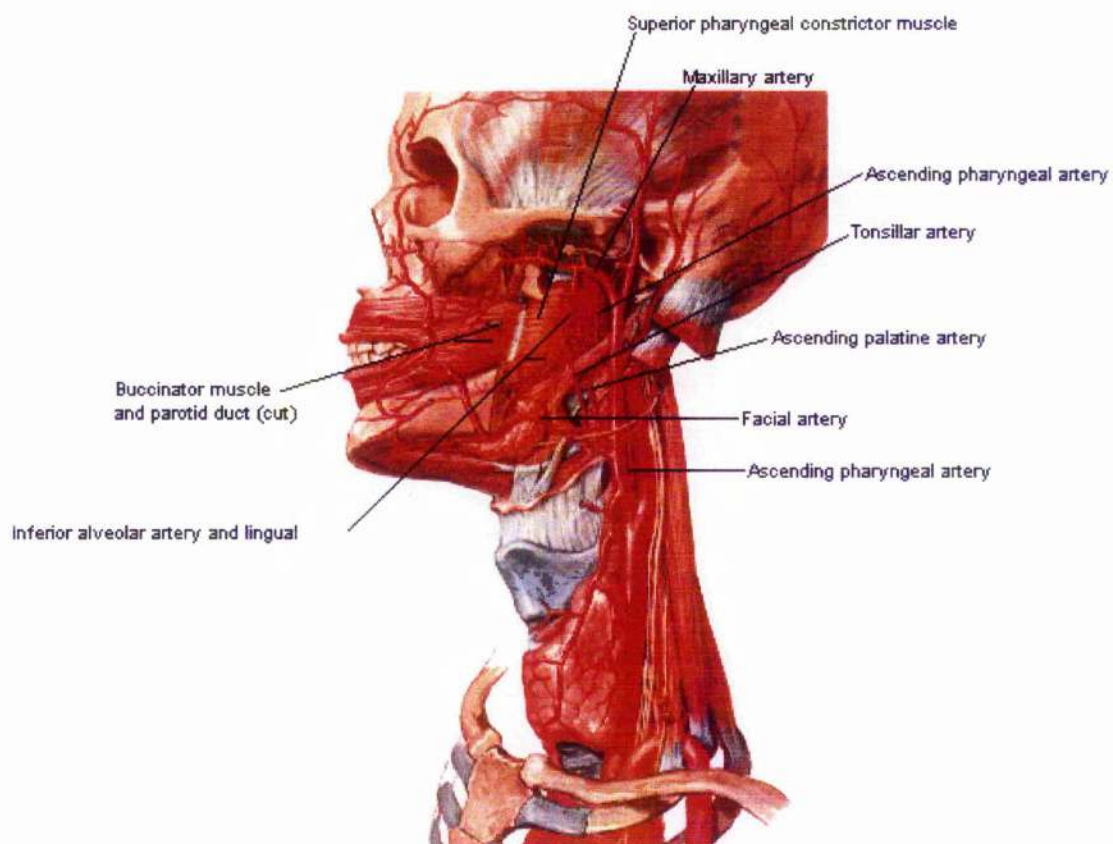


Figure 6 Arteries of Oral and Pharyngeal Regions. (From Netter FH: Interactive Atlas of Human Anatomy, Ciba-Geigy, 1995. Modified by the author)

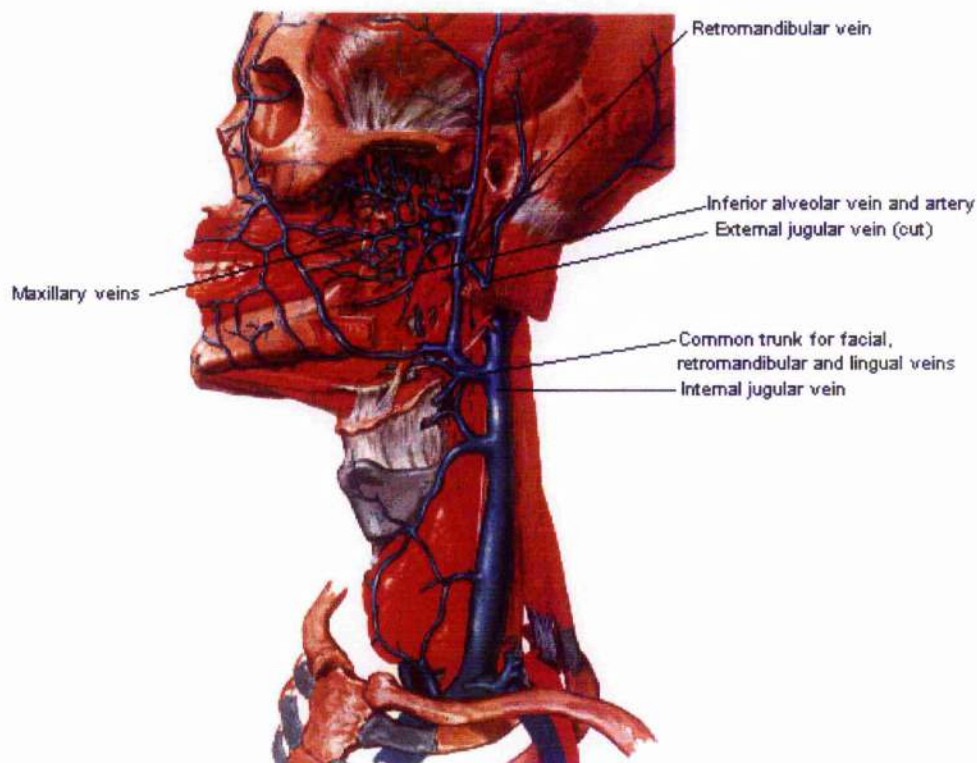


Figure 7 Veins of Oral and Pharyngeal Regions. (From Netter FH: Interactive Atlas of Human Anatomy, Ciba-Geigy, 1995. Modified by the author)

The sensory innervation of the RMT is from branches of the glossopharyngeal (IX) and of the lesser palatine (V2) nerve (Figure 8). The contribution of the IX cranial nerve accounts for the referred ear pain that may be observed in patients with cancer arising in this area (Figure 9).

Afferent Innervation of Mouth and Pharynx

Anterior View

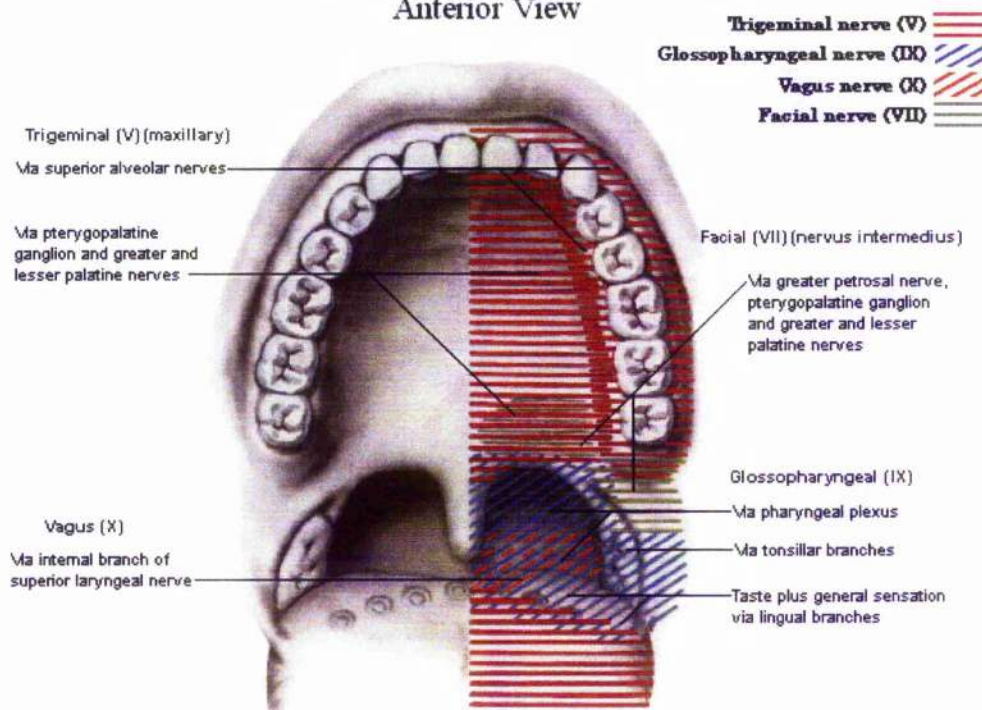


Figure 8 Innervation of mouth and pharynx. (From Netter FH: Interactive Atlas of Human Anatomy, Ciba-Geigy, 1995. Modified by the author)

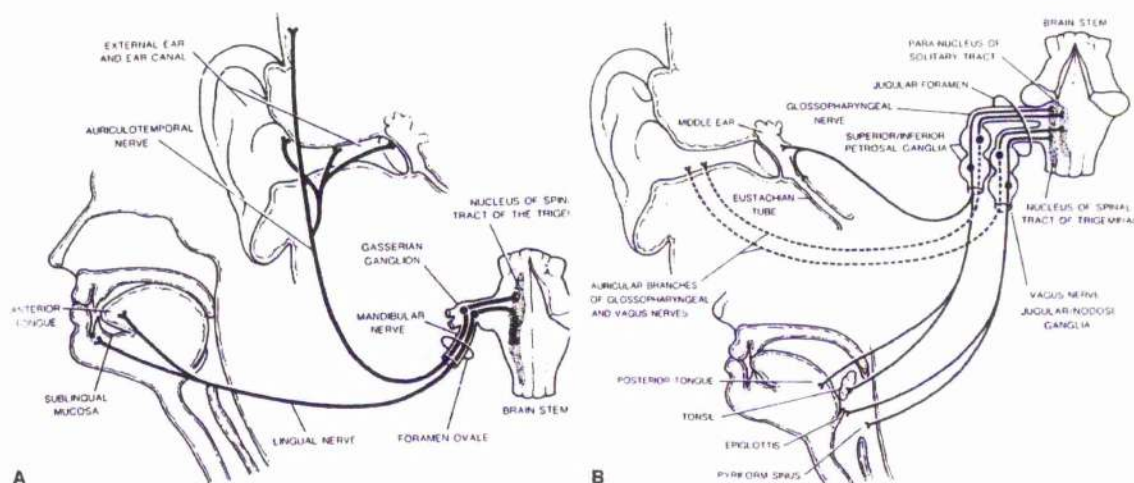


Figure 9 Neural pathways for referred otalgia. A. From floor of mouth and anterior tongue. B. From posterior tongue, oropharynx, and pharynx. (From Lingeman RE and Singer MI: Evaluation of the patient with head and neck cancer. In: Cancer of the Head and Neck. Edited by Suen J and Myers E. New York, Churchill Livingstone, 1981)

The lymphatic drainage of the retromolar trigone is similar to that of the tonsillar fossa, passing to the upper deep jugular chain of lymph nodes. Some lymph channels may also end in the submandibular, in the subparotid and in the lateral retropharyngeal lymph nodes (Figure 10).

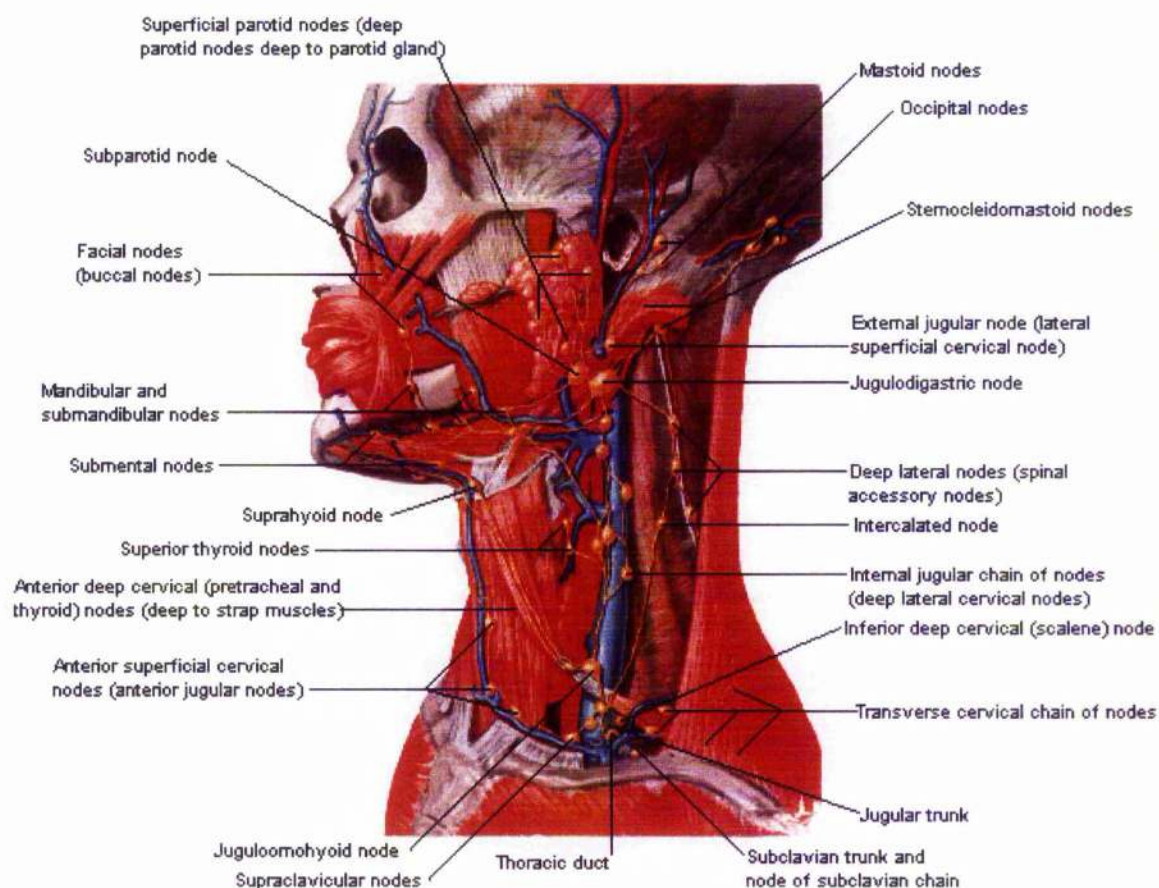


Figure 10 Lymph Vessels and Nodes of Oral and Pharyngeal Regions. (From Netter FH: Interactive Atlas of Human Anatomy, Ciba-Geigy, 1995. Modified by the author)

Pathology

Embryologically, the ectodermally lined stomodeum gives rise to the mucosa of the retromolar trigone, as well as to the mucosa of the lips, buccal mucosa, gingiva, floor of mouth and oral tongue. The mucosa of the RMT is lined by stratified squamous epithelium. It rests on a loose submucosa, which invests salivary glands, blood vessels, and nerves and is permeated by a rich lymphatic system (Figure 11).

The concept of “Step-wise” progression of human cancer has been clinically well recognized. The model of cancer evolution through the accumulation of mutations in both oncogenes and tumour-suppressor genes, and the stepwise selection of more malignant tumour-cell populations, has been widely adopted and generalized to all common forms of cancer, including oral cancer. Progressive epithelial changes in oral mucosa lead to development of hyperkeratosis, dysplasia, carcinoma *in situ* and, eventually, invasive carcinoma. This continuum of progression of epithelial transformation from a normal to a malignant cell may take years in some individuals. On the other hand, such sequential progressive cytologic changes are not observed in all patients and indeed may be absent in many patients with invasive SCC (9).

By far, the most common malignancy arising in the RMT, as in the rest of the oral cavity, is squamous cell carcinoma (SCC) or epidermoid carcinoma, accounting for more than 90%. The remaining malignancies are primarily various types of carcinoma arising from minor salivary glands. The mucoepidermoid carcinoma of the minor salivary glands is more common in the RMT area compared with the adenoid cystic carcinoma, which is the most common malignancy of the minor salivary glands in general(10). Additional rare tumors include lymphomas, melanomas, and a variety of sarcomas (osteosarcoma, fibrosarcoma, rhabdomyosarcoma etc).

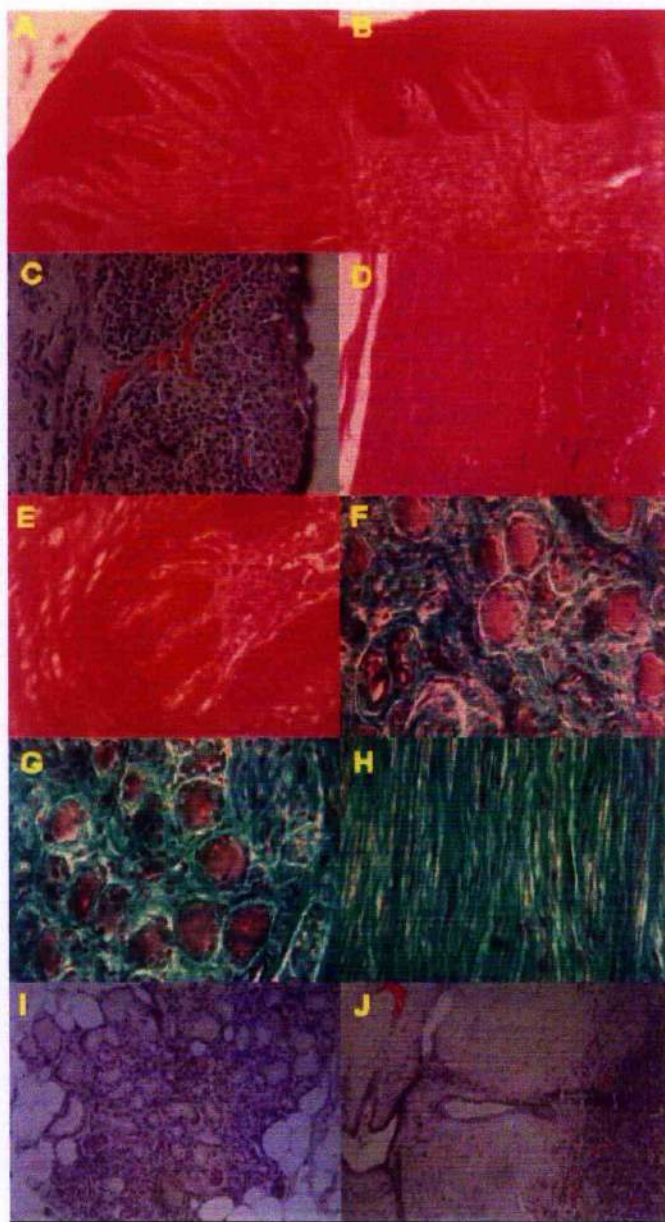


Figure 11 A. Retromolar trigone (RMT) mucosa, B. Hard palate mucosa, C. RMT mucosa from unfixed specimen, D. Buccal mucosa, E. Posterior tongue mucosa, F. Submandibular ganglion, G. Submandibular ganglion, H. Lingual nerve, I. Glandular tissue from RMT of unfixed cadaver, J. Ductal formation from RMT of unfixed cadaver. (photo taken from Stephen J. Goldie's dissertation "The Effect of Surgical Incisions in the Region of the Retromolar Trigone" submitted to the University of Glasgow for partial fulfilment of the BSc (Honours) in Anatomy, 2001)

There are several ways of classifying SCC. Three gross morphologic growth patterns of SCC occur in the RMT area: *exophytic*, *ulcerative*, and *infiltrative*. The most common morphologic types of SCC of the RMT are ulcerative and infiltrative. Exophytic neoplasms are rare (8). Malignancies often display more than one of these manifestations.

The *exophytic* form is least common. It tends to grow more superficially and metastasize later than the other types. This form begins as an area of thickened epithelium, which heaps up and can protrude 1 cm or more above the surrounding mucosa. Ulceration occurs early in its development. Exophytic carcinomas gradually become deeply infiltrative in more advanced cases.

The *ulcerative* type is the most common form of SCC. It begins as a round or oval ulcer with a grey, shaggy base that bleeds readily. Ulcerative types manifest a greater tendency for rapid infiltration and usually have a higher histologic grade than the exophytic type. The ulcer eventually may heap up and become exophytic or remain lower than surrounding mucosa.

Infiltrative malignancies initially appear as a firm mass or plaque covered by mucosa. This type of tumor extends deeply into underlying tissues, with minimal elevation above the surrounding mucosa. As the neoplasm progresses, ulceration and exophytic manifestations may be observed.

Classification by histologic features includes the following varieties (11):

Nonkeratinizing (transitional cell carcinoma, lymphoepithelioma).

Keratinizing.

Verrucous.

Spindle cell (pseudosarcoma, carcinosarcoma).

Adenoid squamous carcinoma (adenoacanthoma, pseudoglandular SCC).

Basaloid squamous carcinoma.

Nonkeratinizing carcinomas tend to arise from respiratory-type mucosa whose cells are endodermally derived and may be well to poorly differentiated. These cancers are frequently associated with a lymphoid tissue stroma that is not an integral component of the tumor. They occur frequently in the nasopharynx, pharynx, and larynx. Nonkeratinizing tumors show mainly submucosal spread and have "pushing" margins in 50% of cases.

Keratinizing SCC occurs in all areas of the upper aerodigestive tract, with the greatest frequency in structures derived from the ectodermally lined stomadeum. In general, these carcinomas are ulcerative or fungating, show infrequent submucosal spread, have sharp infiltrating margins, and are well differentiated in 20% of cases. No differences exist with respect to lymph node metastases or survival based on the feature of keratinisation.

Verrucous Carcinoma. The diagnosis of this interesting but uncommon variant of well-differentiated SCC requires concurrence between the pathologist and the clinician; that is, the diagnosis is clinicopathologic, and microscopic and clinical features must both be consistent with the diagnosis. The lesion is soft and circumscribed at first, but becomes indurated as it advances. This exophytic and warty growth occurs in areas of leukoplakia and consists of well-differentiated keratinized epithelium thrown up into long, papillomatous folds. Histologically, the tumor consists of large, heavily keratinized fronds and downward, sharply projecting, circumscribed, bulbous rete pegs. The border is typically pushing rather than infiltrating. A dense inflammatory reaction occurs in the adjacent stroma. Cytologic features of malignancy (cellular atypia, mitoses) are lacking, and the basement membrane may appear intact.

Biopsies of the surface of the lesion are interpreted repeatedly as benign hyperkeratosis, delaying diagnosis and treatment. The differential diagnosis includes pseudoepitheliomatous hyperplasia, keratoacanthoma, and squamous cell papilloma. Verrucous carcinoma and well-

differentiated SCC with a verrucoid appearance are considered separate entities. Deep biopsy at the base of the lesion is required to show the diagnostic features.

Verrucous "carcinoma" acts in a benign manner. Growth of the primary tumor is indolent, with erosion of underlying structures including bone, but little surface spread. The slow-pushing nature of growth gives few symptoms. This clinical pattern is interesting in view of tissue culture findings, which show that the typical growth pattern is rapid. Indeed, primary tumors can recur rapidly and repeatedly when incompletely excised.

The innocent nature of verrucous carcinoma is further documented by the finding that, although regional lymph nodes can be enlarged, this is presumably caused by an inflammatory response to the heavy keratin deposits rather than by metastatic disease. Distant metastases have never been reported.

Spindle Cell Carcinoma. In this rare variant of SCC, tumors tend to be polypoid or pedunculated masses. Symptoms result from the bulk and anatomic location of the tumors. They are friable, and patients may cough up parts of the tumor or have spotty bleeding. Histologically, spindle cell carcinoma consists of bizarre, spindle-shaped mesenchymal-like cells giving the impression of a highly anaplastic sarcoma with an overlying epidermoid carcinoma. The epidermoid component can be missed unless multiple sections are examined. Electron microscopy supports the classification of spindle cell carcinoma as a variant of SCC with no evidence of malignant degeneration of connective tissue. The carcinoma component is usually small and well differentiated. Tumor metastases are present in 50% of cases, usually in the regional lymph nodes. The metastases may demonstrate the epithelial or spindle pattern or both. The primary tumor tends to remain localized. Low-grade tumors can be treated by wide surgical excision, but poorly differentiated and invasive tumors should probably be treated with planned combined operation and radiotherapy.

Adenoid Squamous Cell Carcinoma. This rare variant of SCC occurs primarily on the vermillion border of the lips and more rarely on the tongue and gingiva. The basic cell is of the keratinising squamous type. This lesion can be distinguished from salivary gland or metastatic tumor by acid mucopolysaccharide stains. The pathogenesis of this lesion is unknown. Adenoid SCCs of the lip are associated with a good prognosis and no regional metastases or deaths. Within the oral cavity, these tumors behave similarly to SCC and have a greater tendency to lymph node metastasis.

Basaloid SCC (BSCC) is an aggressive, histologically distinctive variant of SCC that has a predilection for the upper aerodigestive tract (base of tongue, pyriform sinus, supraglottic larynx) although other sites including the anus, esophagus, and uterine cervix have also been reported. Since its first description in 1986, only about 90 patients have been reported in the English literature.

BSCC tends to occur in older populations, with male predominance. Its aggressive biologic behaviour is characterized by a high incidence of cervical lymph node metastases (64%), distant metastases (44%), primarily to the lungs, liver, bones, brain, and skin, and death from disease: 38% mortality at 17 months median follow-up. The tumors are usually hard and centrally ulcerated, with submucosal infiltration.

Histopathologically, BSCC is distinctive. Microscopically, there is a dual population of cells, and the characteristic growth patterns consist of lobules, nests, and cords of basaloid cells, comedonecrosis, nuclear palisading around the periphery of tumor lobules, small cyst-like spaces surrounding material that resembles mucin, hyalinisation, prominent mitotic activity, and a surface component of dysplastic, in situ or frankly invasive SCC. Some reports note multifocal origin in overlying mucosa. Perineural invasion does not appear to be a prominent feature of the process.

Keratin positivity is seen in the squamous cell component. Studies of oncogene expression in BSCC suggest that it is a distinct variant of SCC characterized by a poorly differentiated cell population.

In BSCC, basaloid and squamous cells are intimately admixed, but the cellular composition is heterogeneous, and establishing the correct diagnosis on biopsy may be difficult or impossible. The two tumors that cause the most difficulty in differential diagnosis are adenoid cystic carcinoma (particularly the solid variant) and small cell undifferentiated (neuroendocrine) carcinoma.(11)

Natural History

Epidemiology

Oral cancer accounts for about 3-4% of all cancers and about 30% of all head and neck cancers. It is the 6th most common cancer in men and the 12th most common cancer in women, prevalence being highest in India. In the UK, oral cancer is estimated to account for 1-4% of all malignancy, with 1900 new cases diagnosed annually (12). Although the most common intraoral site of carcinoma is the tongue, usually on the posterior lateral borders or ventral surfaces, the floor of the mouth is also frequently affected. Together with the retromolar region, these areas comprise a horseshoe-shaped zone of increased cancer susceptibility, accounting for about 75-85% of all cases of intraoral cancer(13;14). According to Jovanovic et al retromolar area accounts for about 11.5% (79/690 patients) of SCC of the lip and oral cavity (15). Shumrick and Quenelle presented that nearly 50% of all carcinomas of the oral cavity and pharynx occur in the palatine arch (including the tonsil), the retromolar trigone, and the adjacent buccal mucosa (16).

Due to the small size of the retromolar trigone, tumors arising here usually involve the adjacent anterior tonsillar pillar, tonsillar fossa, or soft palate. Distinguishing a single site of origin is often impossible; thus many physicians group retromolar trigone cancers with those of the palatine arch. The literature is sparse concerning malignancies specifically arising from the retromolar trigone. In general, tumors with epicenters over the retromolar trigone should be considered to arise from this site(8). Kowalski in his series reported 114 cases in 32 years(17), Byers et al reported 110 cases in 13 years (18) and Huang et al reported 65 cases in 24 years (19).

Cancer of the retromolar trigone is predominantly a disease of elderly men in the sixth and seventh decades of life. According to Byers et al's retrospective analysis of the medical

records of 110 patients seen and treated at The University of Texas M.D. Anderson Hospital and Tumor Institute with biopsy proven squamous carcinoma originating in the retromolar trigone, the average age of the 81 men and the 29 women (male to female ratio 2.8:1) was 62, with a range of 38-85 years(18).

Aetiology

Tobacco and alcohol consumption are the most important risk factors for the RMT carcinogenesis, as they are for the rest of the oral cavity. There is good evidence that tobacco in all forms, including the tobacco in snuff and betel quid (a mixture of ingredients including betel leaf, areca nut, slaked lime, and tobacco, which is wrapped in a betel leaf and chewed), is carcinogenic in the upper aerodigestive tract, which includes the mouth (20). There is fairly convincing evidence that alcohol is also a carcinogen and acts synergistically with tobacco (21). There is little convincing evidence that mouthwash use, poor oral hygiene, or oral infections of viral origin play an important role in the aetiology (22;23). Consuming fruit and vegetables may have a protective effect. There is a slight familial risk for oral cancer, which may be related to the similar exposures to tobacco and alcohol, which occur among family members (24). Table 1 summarises the risks factors of oral cancer.

Byers et al reported in their study that 97% smoked over one pack of cigarettes/day, and 50% were admitted alcoholics (18).

Neoplasms in this area are part of a regional problem of upper aerodigestive tract carcinoma resulting from "field cancerization"(25). Field cancerization was first described in 1953 as histologically altered epithelium surrounding tumor samples taken from the upper aerodigestive tract. Since then, the term has been used to describe multiple patches of pre-malignant disease, a higher-than-expected prevalence of multiple local second primary tumors, and the presence of synchronous distant tumors within the upper aerodigestive tract.

Bilateral cancer in the palatine arch region is not rare, and multiple primary tumors of the aerodigestive tract in general may be as high as 20%.

Normally, saliva provides a protective buffer between toxins and the lining of the mouth because it contains important enzymes that fight and neutralise harmful substances.

Reznick et al in their research demonstrated that the chemicals in tobacco smoke combine with saliva with devastating effect. They destroy the protective components of saliva - leaving a corrosive mix that damages cells in the mouth and can eventually turn them cancerous. Thus, when exposed to cigarette smoke, salivary behavior is reversed and the saliva loses its antioxidant capacity and becomes a potent prooxidant milieu (53).

Marshberg et al, in 1976, assumed the role of saliva as a medium for the carcinogens explaining the distribution of these lesions along the floor of the mouth, side of the tongue, retromolar trigone, and anterior pillar (and their paucity on the hard palate and buccal mucosa) (26).

Table 1 Risk factors of oral cancer

<i>Smoking</i>	2 - 4 times increased risk of developing cancer 90% of patients with oral cancer use tobacco
<i>Marijuana smoking</i>	contains benzopyrene & benzanthrane higher concentration of carcinogens than that in cigarette smoke
<i>Smokeless tobacco (chewing tobacco & snuff dipping)</i>	contains tobacco-specific N-nitrosamines readily extracted into saliva (enhanced in alkaline environments)
<i>Alcohol</i>	2 - 20 times increased risk of developing cancer 75 - 80% of patients with oral cancer consume alcohol
<i>Tobacco & Alcohol</i>	non-drinking smokers: 2 - 4 times increased risk drinking smokers: 6 - 15 times increased risk alcohol: acts as a solvent for carcinogens by enhancing tissue penetration alters epithelial cell metabolism creates nutritional deficiency states or suppresses immunity, causes hepatic cirrhosis and decreases ability to detoxify carcinogens
<i>Habits of third world</i>	bidi, reverse smoking or betel nut chewing
<i>Mechanical trauma</i>	sharp denture flanges, irregular or sharp teeth or restorations, food burn, spicy food, poor oral hygiene & other physical agents
<i>Viruses</i>	papovavirus (including HPV), adenovirus, HSV & EBV, HIV
<i>Impaired immunity</i>	
<i>Other conditions</i>	Candida albicans, syphilis, lupus erythematosus, Plummer-Vinson syndrome, submucous fibrosis, sideropenic dysphagia, actinic keratosis & dyskeratosis congenita

Cancers of the retromolar trigone display biologic properties that more closely resemble SCC of the oropharynx than of the oral cavity. Thus cancer arising from this site most often appears with advanced disease. Approximately 30% to 60% of patients with such malignancies have clinical evidence of regional metastases when first seen. Occult metastases are present in 10% to 20% of patients (16). Metastases occur most commonly to the upper deep jugular (subdigastric) lymph nodes, the submandibular and mid-deep jugular nodes. About 7% of patients develop contralateral metastases. Finding distant metastases at the initial evaluation is rare (16).

Patterns of spread

Due to the high association of alcohol and tobacco abuse and the genesis of SCC of the oral cavity, very often premalignant changes are visible or present before the development of invasive carcinoma.

Most epithelial premalignant changes present as white discoloration (leukoplakia). The risk of development of leukoplakia into invasive carcinoma has been estimated at approximately 4% to 6%. Some patients may manifest premalignant changes by red discoloration (erythroplakia). The risk of development of invasive carcinoma in erythroplakia is as high as 30%.

A varying degree of keratinisation usually is present on the surface of a primary tumor. The extent of keratinisation is a reflection of the degree of differentiation of the underlying malignant process.

Although the current staging system takes into account only the surface dimensions of the tumor, the third dimension (depth of invasion or thickness of the tumor) is important in terms of the risk of regional lymphatic dissemination and prognosis (27). Local extension by spread to adjacent structures may lead to invasion of the underlying soft tissues and muscles, bone, or neurovascular structures.

Local Spread

Local invasion of primary SCCs of the retromolar trigone may extend to the adjacent mucosa, manifesting a zone of invasion with progressive changes demonstrating carcinoma *in situ* and dysplasia in adjacent mucosa. The most common sites of extension are the soft palate, the tonsillar pillar, the lower gum, the buccal mucosa and the floor of mouth.

Extension of the tumor into the depth of the underlying tissues may cause invasion of the buccinator muscle, the superior constrictor of the pharynx, the buccal pad of fat, the masseter muscle, the temporalis muscle and the medial pterygoid muscle.

Further progression of local tumor spread may trigger invasion of neurovascular structures, causing vascular invasion and perineural invasion. The buccal, inferior alveolar and lingual nerves are all easily accessible to cancerous infiltration from the retromolar area. Although

neurotropism is not a classic characteristic of oral SCCs, some patients do manifest neurotropism with extension of tumor along the inferior alveolar nerve into the mandibular canal.

Bone invasion can take place by direct infiltration of the surface lesion into the underlying bone or through the dental sockets into the cancellous part of the mandible and mandibular canal. In edentulous patients, such direct spread may occur through "dental pores" on the edentulous alveolar ridge.(9;28-31)

Another phenomenon unique to the mucosa of the upper aerodigestive tract is field cancerization. Patients with significant exposure to tobacco and alcohol often demonstrate altered mucosa that is highly susceptible to the development of multiple primary cancers. In such patients, varying degrees of epithelial changes may be present, reflecting changes at different stages of development of invasive cancers (32). This process eventually leads to the development of multiple synchronous or metachronous primary carcinomas in the mucosa at risk. The occurrence of multifocal changes, however, is seen in the pharynx more often than in the oral cavity.

Regional Spread

The risk of dissemination to regional lymphatics is related to the size of the primary tumor, the depth of invasion, and the histological grade. The factors that increase the risk of lymphatic dissemination from a primary cancer of the RMT are listed in Table 2.

Table 2 Factors that influence the risk of lymph node metastasis

-
- Size
 - T stage
 - Histomorphologic features
 - Endophytic vs. exophytic
 - Tumor thickness
 - Differentiation (well differentiated vs. poorly differentiated)

Once lymphatic invasion occurs, malignant cells travel through the lymphatics to the first-echelon lymph node (sentinel lymph node), usually situated in the upper deep jugular lymph nodes. The submandibular and mid-deep jugular nodes become involved secondarily. Based on the idea that cancer cells spread in an orderly way from the primary tumor to the sentinel lymph node(s), then to other nearby lymph nodes, sentinel node biopsy is emerging as a successful means of identifying subclinical lymph node disease in mucosal head and neck cancer (54).

Approximately 50% to 60% of patients with retromolar trigone cancer have clinical evidence of regional metastases when first seen. Occult metastases are present in 10% to 20% of patients. About 7% of patients develop contralateral metastases.(16)

Distant Spread

Distant metastases from primary SCCs of the RMT at the time of initial diagnosis are rare. Dissemination to distant sites without local progression or regional spread usually does not

occur. On the other hand, patients with advanced-stage lymph node metastasis (N2 or N3 disease) or those with recurrent disease are at a significant risk of dissemination to distant sites. Distant metastases usually occur in the lung, bones, brain, and other sites.

Clinical Presentation and Diagnosis

Most patients with cancer of the retromolar trigone complain primarily of pain. A persistent sore in the mouth, odynophagia, and a burning sensation when drinking citrus juices are other common symptoms. Referred otalgia may be encountered as the tumor extends medially into the tonsil. Trismus, a mass in the neck, or hearing loss suggests advanced disease. Trismus usually indicates that the neoplasm has infiltrated deeply into the pterygoid musculature. Hearing loss is the result of tumor extension toward the nasopharynx and involving the region of the eustachian tube (8).

The mean duration of symptoms is approximately 5.1 months according to Barbosa (2). Because of its relatively limited surface area, lesions arising in the retromolar trigone frequently invade adjacent areas. The most common sites of extension are the soft palate, the tonsillar pillar, the buccal mucosa, the lower gum and the mandible(17-19). The overall incidence of pathologically proven cancer invading bone is 12-15% (18).

Evaluation of patients with carcinoma of the retromolar trigone involves thorough inspection and palpation as with other sites in the oral cavity. Before instituting therapy, examination under anesthesia and biopsy of all tumors is necessary. While superficial tumor spread seldom evades diagnosis, deep extension can be difficult to diagnose accurately. When malignancy of the RMT extends deeply, patients may experience anesthesia of the mandibular division of the trigeminal nerve or trismus, however the clinical exam does not always accurately reflect the extent of disease. While the presence of trismus suggests pterygoid invasion until proven otherwise, trismus may not necessarily represent direct tumor extension and may result from inflammation of the adjacent pterygoid musculature. Similarly, invasion of the mandible is often under diagnosed on clinical exam. Periosteal and cortical bone invasion is often difficult to assess clinically. Imaging studies such as panoramic radiographs and Computed Tomography (CT) scanning can be helpful if cortical

erosion has occurred however these methods remain imperfect. Lane et al. reviewed the use of CT to assess mandibular invasion and found that bone invasion was not detected in 27% of patients with preoperative scans and that the sensitivity of CT for mandibular invasion was only 50% (55). The failure to accurately diagnose bone invasion preoperatively can have a significant impact on treatment and prognosis upgrading a stage T2 mucosal lesion to a stage T4 lesion. In an effort to improve preoperative diagnostic accuracy, Crecco et al. evaluated 22 patients with SCC of the RMT using 1.5T superconductive Magnetic Resonance Imaging (MRI) to evaluate medullary and cortical bone invasion (56). In this study, preoperative MRI staging correlated with pathological data in 19 of 22 patients resulting in an overall accuracy of 86%. The MRI did not significantly aid in defining mandibular invasion however it provided an excellent method to assess the adjacent soft tissue, including perineural spread and pterygoid involvement. Because the accurate evaluation of tumor extension is critical to treatment planning and prognosis, Genden et al recommend a PANORAMIC radiograph and CT scan for all patients presenting with a tumor of the RMT (57). In those patients that demonstrate trismus, extensive soft tissue involvement, or sensory disturbance, including pain, they include an MRI to assess extent of soft tissue invasion.

Neither fluorodeoxy glucose positron emission tomography (FDG-PET) nor ultrasound has a specific role in the first line investigation of primary head and neck tumours, though they may occasionally be of value in difficult diagnosis.

Malignancies arising from the retromolar trigone frequently spread onto the soft palate, anterior tonsillar pillar, and tonsillar fossa. As the tumor progresses, inferior extension occurs into the tongue base, as well as superior extension toward the maxillary tuberosity. The involvement of the tongue base by neoplasm and the high incidence of multiple primary tumors require endoscopic evaluation, including direct laryngoscopy, oesophagoscopy, and

bronchoscopy, in order to rule out the possibility of synchronous multiple primary carcinomas in the upper aerodigestive tract.

In addition to the evaluation of the primary lesion and assignment of a clinical stage and confirmation of tissue diagnosis, pre-treatment dental evaluation is vitally important in treatment planning. Patients with loose teeth in the proximity of the tumor should not have any dental extractions prior to surgical intervention. Premature extraction of teeth opens up new tissue spaces and raises the risk of further local progression of disease by exposing tooth sockets and opening up the mandibular canal for potential tumor implantation and progression.

The lymph node status of the neck is the most important prognostic factor for patients with head and neck squamous cell carcinoma (HNSCC). There are several important prognostic features like the presence but also number of nodal metastases, level in the neck, size of the nodes, and presence of extranodal spread. If metastases in the neck are diagnosed, the neck should be treated. Because both sensitivity and specificity of palpation are in the range of 60% to 70%, a neck without palpable lymph nodes (N0) is still at risk of harbouring occult metastases. Therefore, much effort has been devoted to increase the accuracy of assessment of the N0 neck. Both CT and MRI of the neck have been found to be superior to palpation in detecting cervical metastases, but still have a relatively low accuracy for the N0 neck. The sensitivity of UltraSound-guided-fine-needle aspiration cytology (US-guided FNAC) in the detection of neck metastases in the N0 neck ranges from 42% by Takes, and 50% by Righi (58), to 73% by van den Brekel et al (59). The specificity is almost 100%, this is because false-positive cytologic results of lymph nodes are very rare. A sensitivity of 73% is significantly better than CT or MRI. A sensitivity of 42% or 50% is inferior to the 60% for CT. The cause of this variation is largely unknown. Where the nodal staging on CT or MRI is equivocal, US-guided FNAC and/or FDG-PET increase the accuracy of nodal staging.

An invasive technique for staging the clinically N0 neck is sentinel node biopsy. The concept of the sentinel node approach is based on the knowledge that nodal metastases progress in an orderly manner with the first site of metastases occurring in the sentinel node. Initial reports on sentinel node biopsy in oral cancer have shown promising results (60). The sentinel node detection technique involves injecting around the primary tumour site with Tc-99m-labelled colloid. The localization of the sentinel node is then performed by planar scintigraphy and the use of a hand-held gamma camera.

Staging

Table 3 & Table 4 lists the criteria for clinical classification of histologically confirmed squamous cell carcinoma of the oral cavity, according to the 1996 American Joint Committee Manual for Staging Cancer 5th edition (3).

Table 3 TNM staging of SCC of the upper aerodigestive tract.

T	x	Tumour size cannot be assessed, e.g. unknown primary
	is	Carcinoma in-situ
	1	Tumour size ≤ 2 cm
	2	Tumour size 2-4cm
	3	Tumour size ≥ 4 cm
	4	Tumour invading deeper structures
N	x	Regional lymph node status cannot be assessed
	0	No nodal metastases
	1	Metastasis in single ipsilateral node, ≤ 3 cm in greatest dimension
	2a	Metastasis in single ipsilateral node > 3 cm but ≤ 6 cm in greatest dimension
	2b	Metastases in multiple ipsilateral nodes, none > 6 cm
	2c	Metastases in bilateral or contralateral nodes, none > 6 cm
	3	Metastasis in a node > 6 cm in maximum dimension
M	x	Distant metastases cannot be assessed
	0	No distant metastases
	1	Distant metastases present

Table 4 Stage Grouping

Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T3N0M0, T1/2/3N1M0
Stage IV	T4N0M0, T4N1M0, anyTN2/3M0, anyT anyN M1

In the sixth edition of the American Joint Committee Manual for Staging Cancer (2002), a uniform descriptor for size for all head and neck sites was introduced (61). In addition, for T4 tumors (larger than 4 cm), subcategories a and b were introduced based on involvement of vital structures and thus their suitability for surgical resection. T4a implies locally advanced but resectable tumor, while T4b implies tumor that is not technically resectable but is suitable for nonsurgical options such as chemoradiotherapy.

For oral cavity:

T4a means that tumor invades adjacent structures (eg, through cortical bone, into deep extrinsic muscle of the tongue genioglossus, hyoglossus, palatoglossus, and styloglossus, maxillary sinus, skin of face). Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4

T4b means that tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

There have been no modifications to the N and M staging system for oral cavity.

Thus, regarding Stage Grouping for oral cavity, Stage IV has been subdivided into:

Stage IVA	T4a N0 M0
	T4a N1 M0
	T1 N2 M0
	T2 N2 M0
	T3 N2 M0
	T4a N2 M0

Stage IVB

T4b Any N M0
Any T N3 M0

Stage IVC

Any T Any N M1

Management

Factors affecting choice of treatment

The factors that influence the choice of initial treatment are those related to the characteristics of the primary tumour (tumour factors), those related to the patient (patient factors), and those related to the treatment delivery team (physician factors). In the selection of optimal therapy, therefore, these three sets of factors for treatment planning require to be considered. Clearly, the goals of treatment are a) curing the cancer, b) preserving or restoring form and function, c) minimizing the sequelae of treatment, d) delivering the optimal treatment in a cost-effective and expeditious manner, and e) preventing second primary tumours(9). To achieve these goals, the currently available therapeutic modalities include surgery, radiation therapy, chemotherapy, and combinations of these for the control of the presenting tumour and for primary and secondary prevention strategies, with lifestyle changes for reducing the risk of multiple primary tumours.

Tumour Factors

The tumour factors that influence the choice of initial treatment are related to size (T stage), invasion of adjacent areas, proximity to bone (mandible or maxilla), status of cervical lymph nodes, and pathology of the primary tumour (histological type, grade, and depth of invasion). In addition to this, any previous treatment rendered to the lesion will influence the choice of therapy.

The size of the primary tumour clearly has a heavy impact on the decision regarding the choice of initial therapy. Small and superficial primary tumours are easily accessible for a relatively simple surgical excision through the open mouth. On the other hand, larger tumours that invade adjacent areas will require more extensive surgical approaches for exposure and excision. In addition to this, with increasing size and the depth of infiltration

of the primary lesion, the risk of regional lymph node metastasis increases, bringing into consideration the need for elective treatment of the clinically negative neck at risk of having micrometastasis.

The histology of the primary tumour is an important parameter that has an impact on selection of initial treatment. Though most SCCs are radioresponsive, those with excessive keratin deposits and verrucous carcinomas are relatively less radioresponsive. The histological grade of the lesion generally reflects the aggressiveness of the tumour. Both poorly differentiated and undifferentiated carcinomas are predictably more aggressive in comparison to moderately well- and well-differentiated carcinomas. However, the most crucial primary tumour histological feature having an impact on selection of initial therapy and eventual prognosis is its depth of infiltration. Thin and superficially invasive lesions that have a lower risk of regional lymph node metastasis, are highly curable, and offer an excellent prognosis. On the other hand, thicker lesions that deeply infiltrate the underlying soft tissues have a significantly increased incidence of regional lymph node metastasis, with its adverse impact on prognosis. Though it would be ideal to know the thickness of the lesion before surgical intervention, in most instances, securing that information prior to surgical excision of the primary tumour is clinically impractical. Therefore, thickness of the lesion as appreciated by palpation, generally is reasonably effective in distinguishing deeply invasive lesions from superficial lesions, in estimating the extent of soft-tissue or bone resection for the primary tumour, and in deciding on the need for elective dissection of regional lymph nodes at risk in the clinically negative neck.

Patients with advanced stage of disease (i.e., those presenting with spread to regional cervical lymph nodes or with large primary tumours, such as T3 and T4) are candidates for consideration of combined modality treatment. Currently, surgical resection followed by postoperative radiation therapy is considered standard treatment for most patients with stage III and stage IV SCCs (9).

Patient Factors

Several factors related to patient characteristics are important in the selection of initial treatment. These are patient's age, general medical condition, occupation, tolerance to treatment, acceptance and compliance with the recommended therapy, lifestyle (smoking and drinking), and socioeconomic considerations. Older age generally is not considered to be a contraindication for implementation of adequate initial surgical treatment. However, with advancing age, intercurrent disease, and debility secondary to associated cardiopulmonary conditions, the implementation of extensive surgical intervention poses increased risk. The ability of the patient to tolerate an optimal therapeutic program is similarly an important facet that can influence the choice of initial therapy. Patient's occupation, acceptance, and compliance for the proposed treatment program are similarly important considerations in planning optimal therapy for the tumor. Patient's lifestyle, particularly with reference to the habit of smoking and drinking, has a heavy impact on the selection and tolerance of the treatment offered. Unwillingness on the part of the patient to give up the habits of smoking and drinking further complicates the administration of adequate treatment and increases the risk of multiple primary tumors. Finally, socioeconomic considerations have started playing an increasing role in the selection and implementation of initial therapy in a cost-effective manner. Allocation of resources required to deliver therapy have to be judged on the basis of outcomes analysis of a particular treatment program. Previous treatment for other lesions in the same area also will influence the decision regarding selection of treatment. For example, radiation therapy previously delivered to the same area for a different lesion may not be available to treat a second tumour in the same area.

Physician Factors

Several physician- and provider-related factors also are important in the selection of initial therapy. These factors are related to the technical and professional skills in surgery, radiation therapy, chemotherapy, rehabilitation services, dental, and prosthetic services and psychosocial support services. Management of oral cancer is a multidisciplinary team effort, and technical capabilities and support services from various disciplines are essential for a successful outcome. A comprehensive head and neck disease management team would consist of the head and neck surgeon combined with other surgical specialties microsurgery, neurosurgery, vascular surgery, plastic and reconstructive surgery, and dental surgery—and prostheses. Similar expertise in radiation oncology (including brachytherapy) is essential for integration of combined treatment programs of external, interstitial, and altered fractionation as well as radiation therapy and chemotherapy. A well-organized team of medical oncologists expert in administration of chemotherapeutic drugs and the management of chemotherapy-related complications is essential in the management of patients with advanced disease and recurrent tumours. Professions allied to medicine such as speech therapy, dieticians, physiotherapists, psychologists, nurse counsellors, social workers, dental hygienists, prosthodontists, maxillofacial laboratory are vitally important for long-term restoration of the quality of life after treatment of oral cancer.

Selection of initial treatment

Since the natural history of tumors in this area is unclear, the optimal treatment remains ill defined. Early reports supported surgical therapy over external beam irradiation (2), however surgical treatment of extensive lesions, particularly those that involve the soft palate and pharynx, can result in significant functional deficits in speech and swallowing. Byers et al reviewed the M.D. Anderson experience in 1984 (18). They reviewed 110 cases of RMT carcinoma, 70 lesions were staged T1—T2, and 77 patients had N0 necks at the

time of diagnosis. The authors reported a recurrence rate of 16% in patients treated with radiation therapy alone and 18% in patients treated with postoperative radiation, and an overall 5-year survival rate of 20%. In this report, Byers et al. concluded that radiation therapy or surgery alone resulted in equivalent disease free survival regardless of the T or N stage (18).

Three years later, Lo et al again reviewed the M.D. Anderson experience of irradiation of anterior faucial pillar-RMT tumors and reported an overall survival of 83%(50). The failure rate was 29% for T1 lesions, 30% for T2, 24% for T3, and 40% for T4 lesions, however after salvage, the ultimate failure rates were 0% for T1 lesions, 6% for T2, 8% for T3, and 20% for T4 lesions. Complications in this series were significant with 30% of patients developing bone exposure.

In 1993, Kowalski et al reported their experience with the extended 'commando' operation for the treatment of RMT carcinoma (17). In this series of 114 patients, 66 patients were treated with postoperative radiation (median 50 Gy) and achieved a 5-year actuarial survival rate of 80% for T1 tumors, 57.8% for T2, 46.5% for T3, and 65.2% in those with T4 tumors. In this study, 27.2% of patients experienced local recurrence; hence the authors recommend postoperative radiotherapy as an adjunct modality in patients with advanced primary tumors and those with metastatic disease at presentation.

More recent literature supports that surgery combined with postoperative or preoperative radiation offers better locoregional control and disease-free survival than radiation or surgery alone (19). Huang et al reported the experience at Washington University with long-term radiation therapy (19). This group reviewed 65 patients who were treated with preoperative radiotherapy (15%), postoperative radiotherapy (60%), or radiation therapy alone (23%) and found a 5-year disease free survival rate of 90% with preoperative radiation, 63% with postoperative radiation, and 31% with radiation alone. On multivariate

analysis, Huang et al concluded that N stage had a significant impact on disease free survival and rates of distant metastasis. In contradistinction to these findings, the Radiation Therapy Oncology Group demonstrated no significant difference in 4-year overall survival and locoregional control in a randomized study of different treatment modalities (62). In this series of 70 patients randomized to preoperative radiation (30%), postoperative radiation (36%), and definitive radiation (33%), locoregional control was 43, 52, and 38%, respectively.

Similar to previously published reports, margin status is the most significant predictor of locoregional control (63-65) and nodal status has the most significant impact on distant metastasis, and hence disease-free survival (66). Consistent with these observations, the addition of radiation therapy, either preoperatively or postoperatively, confers a significant survival advantage for patients with carcinoma of the RMT.

The treatment decisions in the management of RMT depend upon the stage at presentation, the patient's general medical condition and symptomatology and the proximity of the lesion to the mandible. Small stage I tumours can be managed equally well by surgery only or radiotherapy only. Stage I tumours managed by surgery are reconstructed with local flaps or split-thickness skin grafts. Larger stage II neoplasms frequently require resection of portions of the soft palate, which increases morbidity from the standpoint of speech and deglutition. In general, radiotherapy only does not cure the deeply infiltrating cancers that cause trismus. These lesions should be treated surgically.

Stage III and IV cancer of the retromolar trigone should be managed by combined surgery and radiotherapy.

Accurate and individualized estimation of survival in patients with HNSCC would undoubtedly lead to an improvement in therapeutic and care strategies, minimizing risks of under-treatment and over-treatment. Baatenburg et al developed a statistical model in which

the prognostic value of age, gender, site of the primary tumor, T-, N-, and M-stage, histological data, molecular biology markers, prior malignancies and other prognostic factors, are integrated to predict survival probabilities (67). All these data of a newly diagnosed patient with HNSCC are entered in a dedicated computer software program, called OncologIQ[®], which immediately calculates and displays the survival curve for that individual onscreen. This would allow for a more precise and individual prediction of outcome in HNSCC patients. Therefore, this model may help in clinical decision making and appropriate counseling of patients with HNSCC.

Surgical approaches

A variety of surgical approaches (oral approach, mandibulotomy approach, lower cheek flap approach, visor flap approach, upper cheek flap approach) as shown in Figure 12, are available for access in the oral cavity.

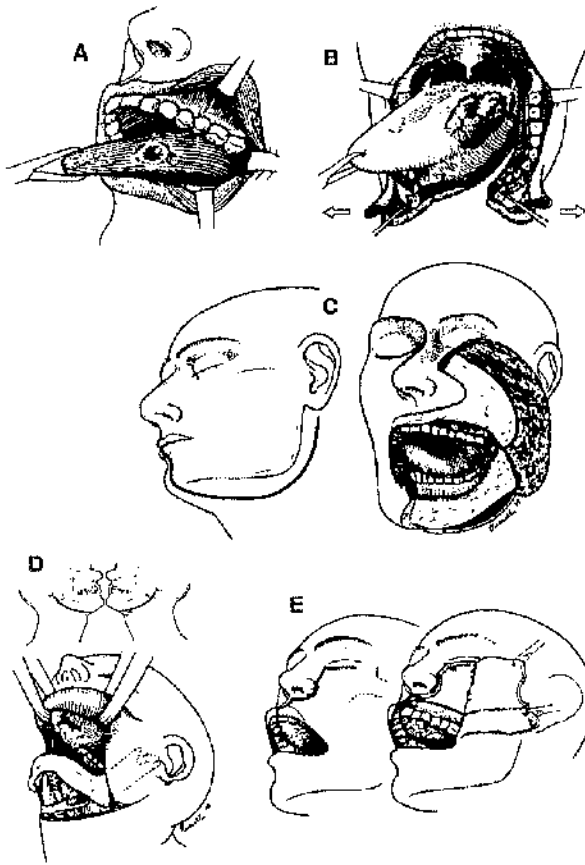


Figure 12 Surgical approaches to carcinoma of the oral cavity. (A) Oral approach. (B) Mandibulotomy approach. (C) Lower cheek flap approach. (D) Visor flap approach. (E) Upper cheek flap approach. (Reproduced from Shah JP. Head and neck surgery, 2nd ed. London: Mosby-Wolfe, 1996.)

Small superficial primary lesions of the retromolar trigone can be excised via an oral approach. Most of the lesions of that area require a mandibulotomy approach (Figure 13).

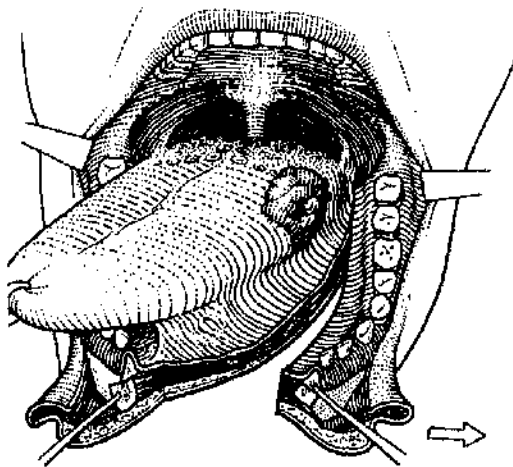


Figure 13 Mandibulotomy (Reproduced from JP Shah. *Head and neck surgery*, 2nd ed. London: Mosby-Wolfe, 1996.)

A typical resection (including 1 cm margins around the tumour) includes the retromolar trigone, the tonsillar fossa, and a portion of the floor of the mouth, soft palate, and buccal mucosa. The majority of the pterygoid musculature should be included with the specimen. Tooth extraction at the anterior bone resection margin permits saw cuts through tooth sockets, which prevents injury to adjacent tooth roots. Preserving as much of the mandible body as is oncologically prudent will decrease the resulting functional and cosmetic deformity.

Management of the mandible

Primary carcinomas of the oral cavity extend along the surface mucosa and the submucosal soft tissues and approach the attached lingual, buccal, or labial gingiva. From this point onward, the tumour does not extend directly through intact periosteum and cortical bone toward the cancellous part because the periosteum acts as a significant protective barrier. Instead, the tumour advances along the attached gingiva toward the alveolus. In patients

with teeth, the tumour extends through the periodontal ligament into the cancellous part of the bone. In edentulous patients, the tumour extends up to the alveolar process and then infiltrates the bone defects in the alveolar process and thence extends to the cancellous part of the mandible (28;30;31). Therefore, in patients with tumours close to the alveolar crest of the mandible (or even those demonstrating early invasion of the mandible), marginal mandibulectomy (Figure 14) is feasible, as the lower cortex of the mandible inferior to the roots of the teeth remains uninvolved and can be spared.

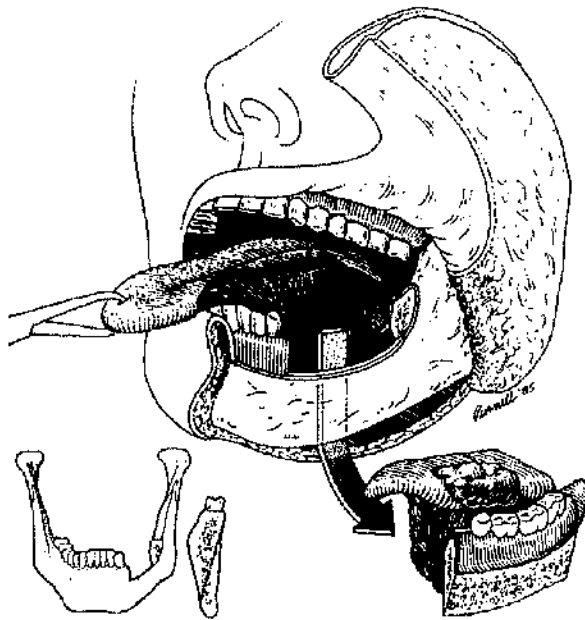


Figure 14 Marginal mandibulectomy. (Reproduced with permission of the author and publisher from JP Shah. *Head and neck surgery*, 2nd ed. London: Mosby-Wolfe, 1996.)

In edentulous patients, however, the feasibility of marginal mandibulectomy depends on the vertical height of the mandible. With aging, the alveolar process recedes, and the mandibular canal gets closer and closer to the alveolar surface. Resorption of the alveolar process eventually leads to a "pipestem mandible" in very elderly patients. The ability to perform a satisfactory marginal mandibulectomy in such patients is nearly impossible, owing to the risk of iatrogenic fracture intraoperatively or spontaneous fracture in the postoperative period due to weakening and avascularity of the residual mandible.

When tumour extension involves the cancellous part of the mandible, a segmental mandibulectomy (Figure 15) must be performed. Segmental mandibulectomy also may be required in patients who have massive primary tumours close to the mandible and significant soft-tissue disease adherent to or surrounding the mandible.

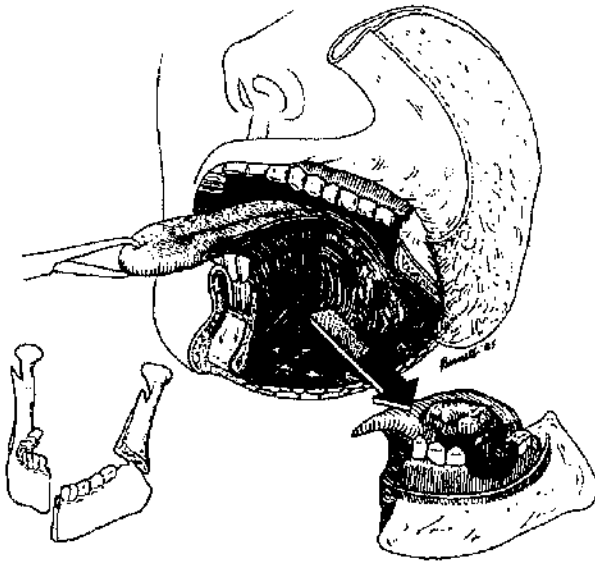


Figure 15 Segmental mandibulectomy. (Reproduced from JP Shah. Head and neck surgery, 2nd ed. London: Mosby-Wolfe, 1996.)

However, segmental mandibulectomy never should be considered simply to gain access to the primary oral cavity tumour that is not in the vicinity of the mandible.

The in-continuity tumor excision with mandibulectomy and neck dissection is called "commando operation" ("Com.m.a.n.d.o." stands for "**COM**bined **M**andibulectomy **A**nd **N**eck **D**issection **O**peration"). The concept of the commando operation needs to be redefined, as no lymphatic channels pass through the mandible, therefore not warranting the need for an in continuity composite resection of the uninvolved mandible.

Management of the neck

Treatment of the regional lymph nodes is an integral component of the management of patients with squamous cell carcinoma (SCC) of the head and neck region. For several decades since the beginning of this century, surgical treatment of cervical metastases consisted of radical neck dissection (RND) as described by Crile (33) in 1906 and popularised by Martin et al. (34) during the 1950s. During the last 20 years, significant changes have occurred in the treatment of the neck. As a result, today RND is not the only operation used for surgical treatment of the neck, and surgery is not the only treatment for every patient with cervical lymph node metastases. A recent review of neck dissection terminology was performed by Robbins (35) in which he outlined the consensus report on neck dissection terminology by the American Academy of Otolaryngology – Head and Neck Surgery. These more accurate and descriptive terms are used throughout this Thesis and the terminology is summarised in Table 5, Figure 16 and Table 6.

Table 5 Neck dissection levels

Level of Neck Dissection	Anatomical Description
I	Submandibular triangle and Submental triangle. Anatomical borders: lower border of the mandible and the bellies of the digastric muscle; hyoid bone and the midline.
II	Upper jugular nodes. Anatomical borders: skull base to bifurcation of common carotid artery at the level of the hyoid bone; lateral border of sternohyoid muscle to posterior border of sternocleidomastoid.
III	Middle jugular: Anatomical borders: inferior border of level II to the omohyoid muscle at the level of the cricothyroid membrane; lateral border of sternohyoid muscle to posterior border of sternocleidomastoid.
IV	Lower jugular: Anatomical borders: from the inferior border of level III to the clavicle; lateral border of sternohyoid muscle to posterior border of sternocleidomastoid.
V	Posterior triangle

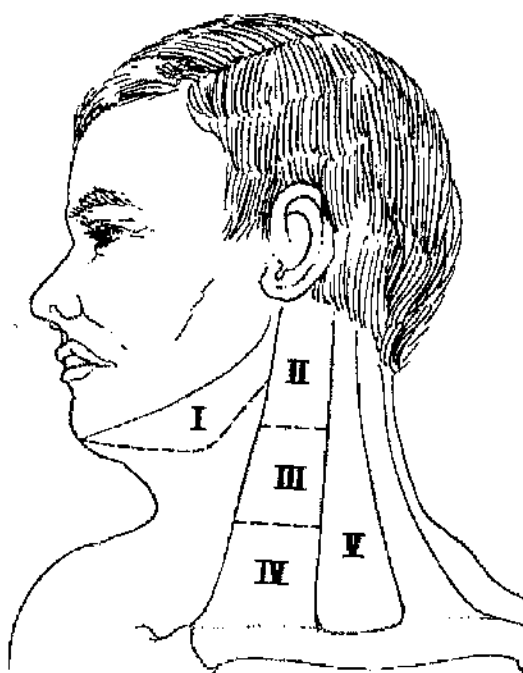


Figure 16 Levels of lymph nodes

Table 6 Neck Dissection Terminology

Terminology	Description
RND	Radical neck dissection excising levels I-V, including the SAN, IJV and SCM
MRND-I	Excising levels I-V, including the IJV and SCM
MRND-II	Excising levels I-V, including the IJV
MRND-III	Excising levels I-V, all three non-lymphatic structures spared
Selective Neck Dissection	Excision of up to four levels of cervical nodes, usually sparing some or all non-lymphatic structures
SOHND	Supraomohyoid neck dissection, excising levels I-III, sparing all non-lymphatic structures
Anterolateral Neck Dissection	Excision of levels I-IV
Posterolateral Neck Dissection	Excision of levels II-V
Extended Neck Dissection	Excision of levels I-V with further dissection continued to deeper structures (e.g. pharyngo-laryngeal nodes, tracheo-oesophageal nodes, parotid nodes, etc)

The consensus report on neck dissection terminology states that a RND is as described by Crile, excising the lymph nodes in levels I-V and including the spinal accessory nerve (SAN), sternocleidomastoid muscle (SCM) and internal jugular vein (IJV). Those procedures in which all five levels of nodes are excised but one or more of the three non-lymphatic structures are spared are called modified radical neck dissections (MRND). A neck dissection, which leaves one or more of the nodal tissue from levels I-V within the neck, is called a selective neck dissection, and usually spares the IJV, SAN and SCM. Selective neck dissections may be described according to the levels that are removed or may be termed descriptively.

More than ever before, appropriate management of the cervical lymph nodes requires a good understanding of the incidence, patterns, and prognostic implications of lymph node metastases and of the role of combined surgery, radiation therapy, and chemotherapy in the treatment of the neck in cancer patients.

Incidence of cervical metastases

The propensity of SCCs of the upper aerodigestive tract to metastasise to the cervical lymph nodes varies depending on the site of origin of the lesions and on size or tumour (T) stage. Lindberg's (36) classic incidence figures (based on the presence of palpable lymphadenopathy in more than 2,000 patients with SCC of the head and neck) have been refined by the studies of Byers et al. (37) and Shah (38), in which a large number of neck dissection specimens were evaluated (Table 7 & Table 8). From these observations, it is clear that carcinomas of the retromolar trigone have a relatively high propensity to metastasise to the lymph nodes. The rate of occurrence of lymph node metastases in patients with small (T1 and T2) and large (T3 and T4) tumours is between 35% and 65%.

Table 7 Incidence of lymph node metastases (based on physical examination)

Site of primary tumour	Percentage of necks with <u>nodal metastases</u>			
	T1	T2	T3	T4
Oral cavity				
Oral tongue	0.14	0.30	47.50	76.50
Floor of mouth	0.11	0.29	43.50	53.50
Retromolar trigone	11.50	37.50	0.54	67.50
Oropharynx				
Tonsil	70.50	67.50	0.70	89.50
Base of tongue	0.70	0.71	74.50	84.50
Pharyngeal walls	0.25	0.30	0.67	0.76
Larynx				
Glottic	0.39	41.50	64.50	0.59
Supraglottic	0.63	69.50	0.79	73.50
Hypopharynx	92.50	84.50	88.50	0.83

Table 8 Incidence of histopathologic lymph node metastases

Site of primary tumor	T1-2	T3-4
Oral cavity		
Oral tongue	18.6	31.6
Floor of mouth	18.6	26.3
Lower gum	11.5	13.3
Buccal mucosa	—	—
Retromolar trigone	36.4	33.3
Oropharynx		
Tonsil	—	—
Base of tongue	—	50.0
Pharyngeal walls	20.0	62.5
Larynx		
Glottic	21.4	14.0
Supraglottic	30.8	25.0
Hypopharynx		
Pyriform sinus	66.7	55.2

Anatomic and radiographic studies of the lymphatics of the head and neck have demonstrated that the lymphatic drainage of the different areas of the upper aerodigestive tract occurs along predictable pathways (39). Furthermore, clinical studies (38) have demonstrated that tumours from these areas metastasise to the lymph nodes following the same pathways, at least as long as the neck has not been treated previously with surgery or radiation therapy (Table 9). A now commonly accepted concept is that the lymph node groups that harbour metastases most often in patients with carcinomas of the oral cavity are the submental (Ia), submandibular (Ib), upper jugular (II), and midjugular nodes (III). From these, the submandibular (Ib) and upper jugular (II) lymph nodes are the most commonly involved in the retromolar trigone cancers.

These patterns of distribution have been shown convincingly to occur both in patients who are staged NO clinically and are found to have occult metastases and in patients with palpable, histologically proved lymph node metastases (38).

Controversies exist amongst clinicians as to which type of neck dissection is most appropriate for varying disease patterns. The more radical the dissection, the greater the likelihood of significant morbidity arising from the procedure. Conversely, the less nodal tissue removed, the more likely it is to leave nodal tissue infiltrated with malignancy. Also, sparing of non-nodal structures is technically more demanding than a traditional RND, and therefore increases the time spent by the patient under general anaesthesia.

Regarding the retromolar trigone cancer treatment protocol at Canniesburn Hospital, patients with a clinically positive neck underwent a therapeutic neck dissection, if possible a MRND type III. Most of the patients with a clinically negative neck underwent elective neck dissection, for better access to the primary tumour, reconstruction requirements or cases

Table 9 Pattern of nodal metastases

Primary site	Percentage of nodal involvement					
	IA	IB	II	III	IV	V
Oral tongue	3.3 ^a	22.8	59.7	10.7	2.6	7.0
	9.0 ^b	18.0	73.0	18.0	—	—
	— ^c	14.0	19.0	16.0	3.0	—
Floor of mouth	4.3 ^a	43.1	37.1	9.5	4.3	1.7
	7.0 ^b	64.0	43.0	—	—	—
	— ^c	16.0	12.0	7.0	2.0	—
Buccal mucosa	— ^a	—	—	—	—	—
	— ^b	—	—	—	—	—
	— ^c	44.0	11.0	—	—	—
Lower gum	— ^a	—	—	—	—	—
	— ^b	60.0	40.0	—	—	—
	— ^c	27.0	21.0	6.0	4.0	2.0
Retromolar trigone	0.6 ^a	17.1	61.8	16.4	3.3	0.6
	— ^b	25.0	63.0	12.5	—	—
	— ^c	19.0	12.0	6.0	6.0	0.0
Supraglottic larynx	0.5 ^a	1.0	47.6	34.0	10.7	6.3
	— ^b	—	48.0	38.0	5.0	—
	— ^c	6.0	18.0	18.0	9.0	1.5
Glottic larynx	— ^a	—	—	—	—	—
	— ^b	—	55.0	27.0	—	—
	— ^c	—	21.0	29.0	7.0	7.0

^aBased on clinical examination (3).^bBased on examination of selective neck dissections (4).^cBased on examination of radical neck dissections (63-65).

deemed at high risk for developing cervical metastasis. Sparing of as many non-nodal structures as possible for functional preservation remains one of the principles of the

Canniesburn management philosophy, especially in the management of the clinically N0 neck.

Reconstruction

Reconstruction of the oral cavity is essential in order to restore function and as much as possible make it aesthetically pleasing.

Following the concept of the reconstructive ladder, healing by secondary intention, primary closure, skin grafts (full or split thickness) and flaps (random, axial, myocutaneous, fasciocutaneous and free flaps) are the available reconstructive options. Primary closure, skin grafting and random flaps (buccal, tongue flaps) are feasible only for very small and superficial tumors.

Larger defects of the retromolar trigone require most often the use of a free flap or a pedicled flap for closure. Pectoralis major myocutaneous flap was and, in some places without microsurgery facilities, still is the workhorse for reconstruction.

Radial forearm and anterolateral thigh fasciocutaneous free flaps are the most commonly used free flaps for reconstruction of the retromolar trigone area. Other less often used free flaps are the scapular, the lateral arm and the latissimus dorsi.

When the mandible needs to be reconstructed the most common osteocutaneous donor sites are the fibula, the ilium, the scapula and the radius.

Radiotherapy

The goal of treatment for most cancers is to provide the best chance of cure. For early lesions of the oral cavity, either radiotherapy (RT) or surgery produces similar rates of local control, regional control, control above the clavicles, and 5-year cause-specific survival.

However, the treatments may have substantially different morbidities and may result in differences in quality of life. Approximately 90% of head and neck cancer patients are 50 years of age or older and often have other medical problems. In this age group quality of life is often the most important consideration in selecting treatment modality. It is desirable to avoid combining surgery and radiotherapy for the treatment of early primary tumours, and a choice must therefore be made between the two modalities.

For some sites (floor of the mouth, oral tongue), primary surgical resection is preferred because it reduces the risk of radiation complications while for other sites (retromolar trigone, gingiva, buccal mucosa, hard palate) radiotherapy is preferred because of its greater efficacy (40).

Although used less frequently than in the past, radiotherapy still has a role for patients with early primary lesions of the oral cavity if the patient refuses surgery or is medically inoperable. In these cases, the radiation oncologist must have the technical capability and knowledge of the appropriate time dose factors necessary to produce cure with a minimum of complications.

Most primary lesions of the retromolar trigone, whether early or advanced, are currently managed by resection initially. Radiotherapy is relatively unsuccessful in the control of retromolar trigone tumours when used exclusively. A combined-modality approach increases the five-year survival rates and offers better locoregional control and disease free survival (19;41).

After review of the pathologic specimen, patients may receive postoperative radiotherapy if certain adverse histological features are detected (positive margins, close (<0.5 cm) margins, dysplasia or carcinoma in situ at the margins, vascular space invasion, perineural invasion, bone invasion, extension into the soft tissues of the neck, involvement of multiple lymph

nodes (especially with multiple levels of involvement), or extracapsular extension from lymph node metastases).

Preoperative radiotherapy is given when the patient has a fixed neck node or if the primary cancer extensively involves the dermal lymphatics, which have no valves and therefore may allow spread of cancer in many directions. Radiotherapy may also be used in palliation.

Radiotherapy Technique

Small lesions of the retromolar trigone may be managed by intraoral cone radiotherapy for all or part of the therapy. Well-lateralized lesions of the retromolar trigone may be treated by ipsilateral mixed beam techniques. An intraoral lead shield reduces the radiation dose given to the contralateral mucosa.

Patients receiving radical postoperative radiotherapy at Canniesburn Hospital were prescribed 60 Gy in 30 fractions over 6 weeks, commencing within 6-8 weeks of surgery. The oral cavity and anterior triangles of the neck were treated using a half-beam arrangement (42). The oral cavity was treated where possible using a wedged pair to spare the contralateral parotid and minimize long-term xerostomia.

Materials and Methods

Cadaver Preparation

Bodies donated to the Department of Anatomy at Glasgow University are routinely embalmed through the carotid artery with a commercial embalming fluid. By modifying dissections described in "Cunningham's Manual of Practical Anatomy" (43), "Grant's Atlas of Anatomy" (44) and "A new system of Anatomy" (45) and employing standard dissection techniques and instruments the gross anatomy of the RMT and surrounding areas were revealed. The author used forceps, scalpels with size 23 and 15 blades, and a small pair of scissors, available in any basic dissection kit. The specimen was dissected in layers, beginning with the removal of the mucosa.

It was decided that the excision of a T2 sized tumour would be the most appropriate operation to imitate, as this is the most common size of a tumour. T2 tumours are 2-4cm in diameter. The tumour site was marked on the RMT with a black marker pen. The resection margins were marked with a purple marker pen; approximately 1cm all round the pseudotumour (see Figure 17). The head was split in half with a power saw. The aim of this dissection was to find out the anatomic structures in danger when performing a retromolar trigone tumor excision.

Photographs were taken using a digital camera, Nikon Coolpix 990. The photographs were processed in Adobe Photoshop 6.0.



Figure 17 T2 sized 'Pseudotumour' marked in black ink; Resection margin marked in purple ink

Retrospective case analysis

The Oral Pathology Unit in Glasgow Dental Hospital and School maintains a disease index of reported cases. From this it was possible to retrieve the pathology numbers of cases diagnosed as oral squamous cell carcinomas that were received and reported between 1st January 1985 and 31st December 1999. From the case numbers retrieved, it was possible to obtain the pathology report form of each case and this provided the name of the patient and the hospital record numbers. Having this information it was possible to look at the patient name index, as for each patient a separate card with all the related pathology report numbers is maintained. Thus it was possible to access all the pathology reports related to individual patients. Having the hospital numbers of these patients, their medical records were retrieved from Canniesburn's Medical Records Department.

The criteria used to include patients in this study were strict, demanding many times an arbitrary decision as to the site of origin, particularly with large lesions involving many adjacent sites. Large lesions involving many adjacent sites were included in the study if the epicenter of the lesion was in the retromolar trigone. Patients with lesions invading the retromolar trigone area from adjacent sites were excluded. The patients were included if they were previously untreated, had a biopsy proven squamous cell carcinoma reviewed by our pathologist and the minimum follow up was 2 years.

From a database of 1404 cases diagnosed as oral squamous cell carcinoma, 199 had the retromolar trigone area involved. From these patients only 113 fulfilled the above mentioned criteria. From these 113 patients with histologically proven squamous cell carcinoma of the retromolar trigone, treated at Canniesburn Hospital, Glasgow between 1985 and 1999, the clinical presentation, therapy, pathological staging, patterns of loco-regional and systemic failure and survival were retrospectively analyzed. All the data were input and processed in a specially designed software application for Head and Neck, called Infoflex by Cameleon.

The follow-up period ranged between 2 and 10 years. Ten patients with inadequate follow-up data and patients who died of unrelated causes during the follow-up period were included in the survival analysis up to the time of their loss to follow-up or death and excluded thereafter, according to the Kaplan-Meier method. Five patients who underwent palliation only as the treatment modality were excluded from the survival analysis.

Statistical analysis was performed by using the SPSS for windows, version 10.1, computer program (SPSS Inc, Chicago,IL). The probabilities of determinate 5-year survival rates were calculated by the Kaplan-Meier method. To test the statistical significance of differences between curves, the log-rank test was used. The statistically significance correlation between length of symptoms and T stage of tumour was evaluated by using Kendall's rank correlation coefficient tau-b (τ) test. A significance level of .05 was used for all statistical tests.

Results

Anatomy

Figure 18, Figure 19 and Figure 20 demonstrate the gross anatomy of the RMT and surrounding region. Superior to the RMT, forming the roof of the oral cavity is the hard and soft palate. Laterally is the buccal mucosa and medially the tonsillar fossa, the floor of the mouth and the posterolateral part of tongue.

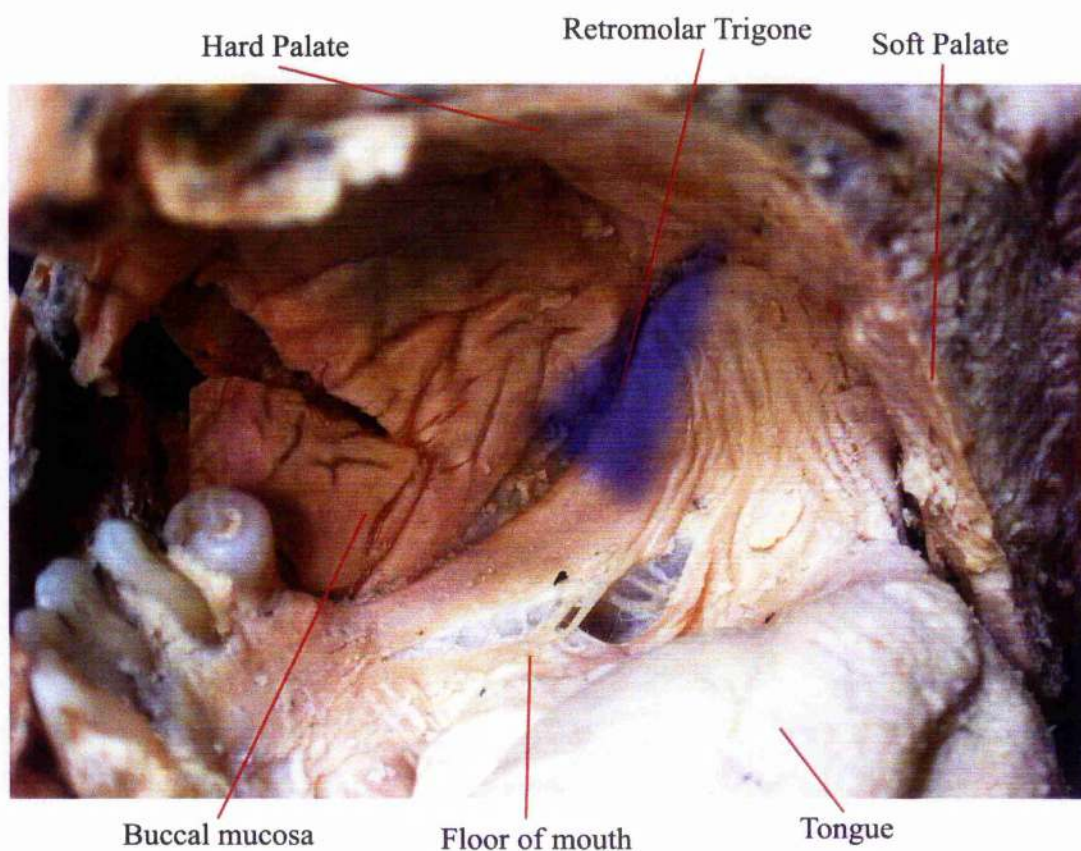


Figure 18 Retromolar trigone area (shadowed area).

After stripping the mucosa, the buccinator muscle and the superior constrictor of the pharynx connected with the pterygomanibular raphe came into sight. The buccopharyngeal fascia lay immediately below the buccinator muscle and the superior constrictor of the pharynx separating them from the buccal pad of fat. Deeper dissection revealed the masseter

muscle and the anterior border of the ascending ramus, almost all of which were invested by the tendinous insertion of the temporalis muscle. Crossing this border was the buccal nerve. Medially lay the anterior edge of the medial pterygoid muscle. In the acute deep angle formed by the medial pterygoid and the ascending ramus, which is open superiorly, ran the two branches of the mandibular nerve - the inferior alveolar and the lingual nerve. These three nerves – the buccal, inferior alveolar and lingual – were all at risk in the usually required margins of a retromolar trigone tumour excision.

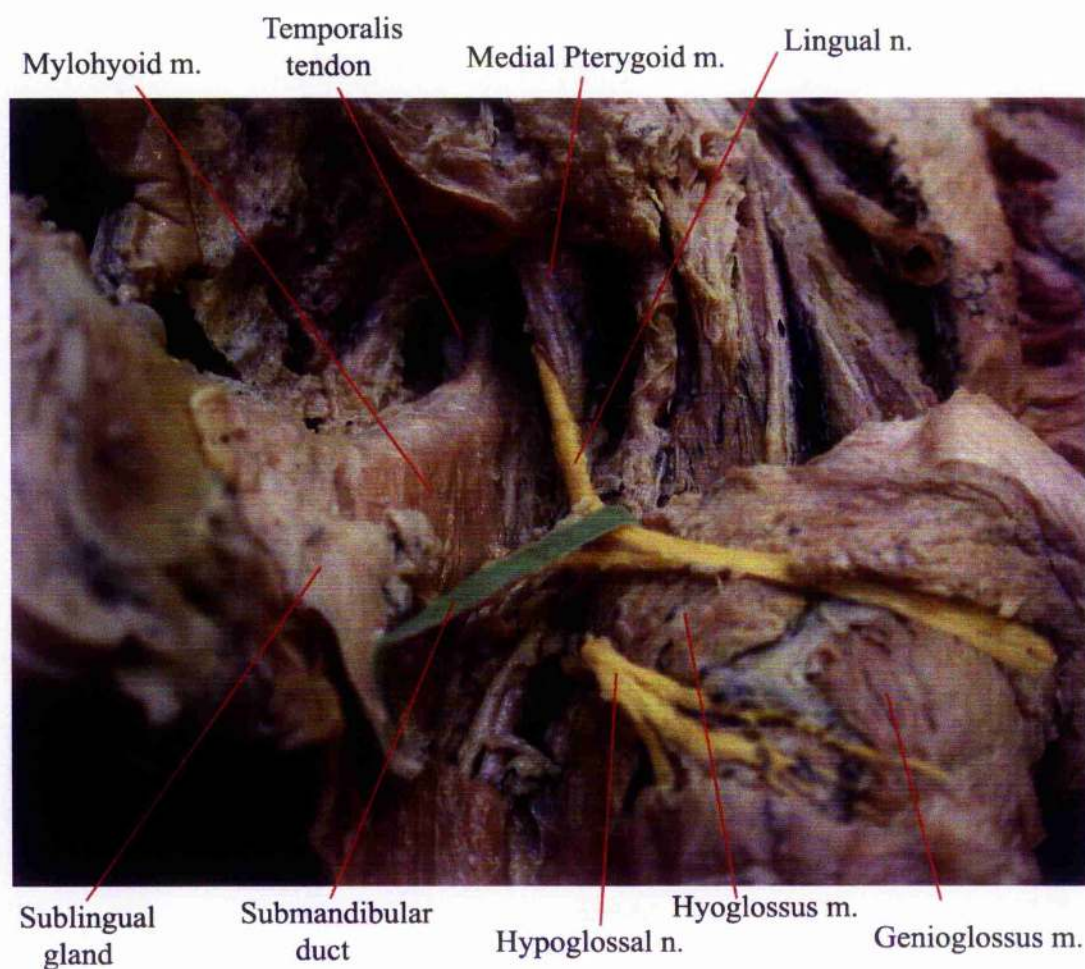


Figure 19 Gross anatomy of the Retromolar trigone.

Having removed the mucosa over the floor of mouth and reflecting genioglossus from its attachments on the mandible, this allowed an excellent view of the sublingual and

submandibular gland with its duct. The submandibular duct is another structure that could be traumatised during excision of RMT tumors, especially the ones that invade the lateral floor of mouth.

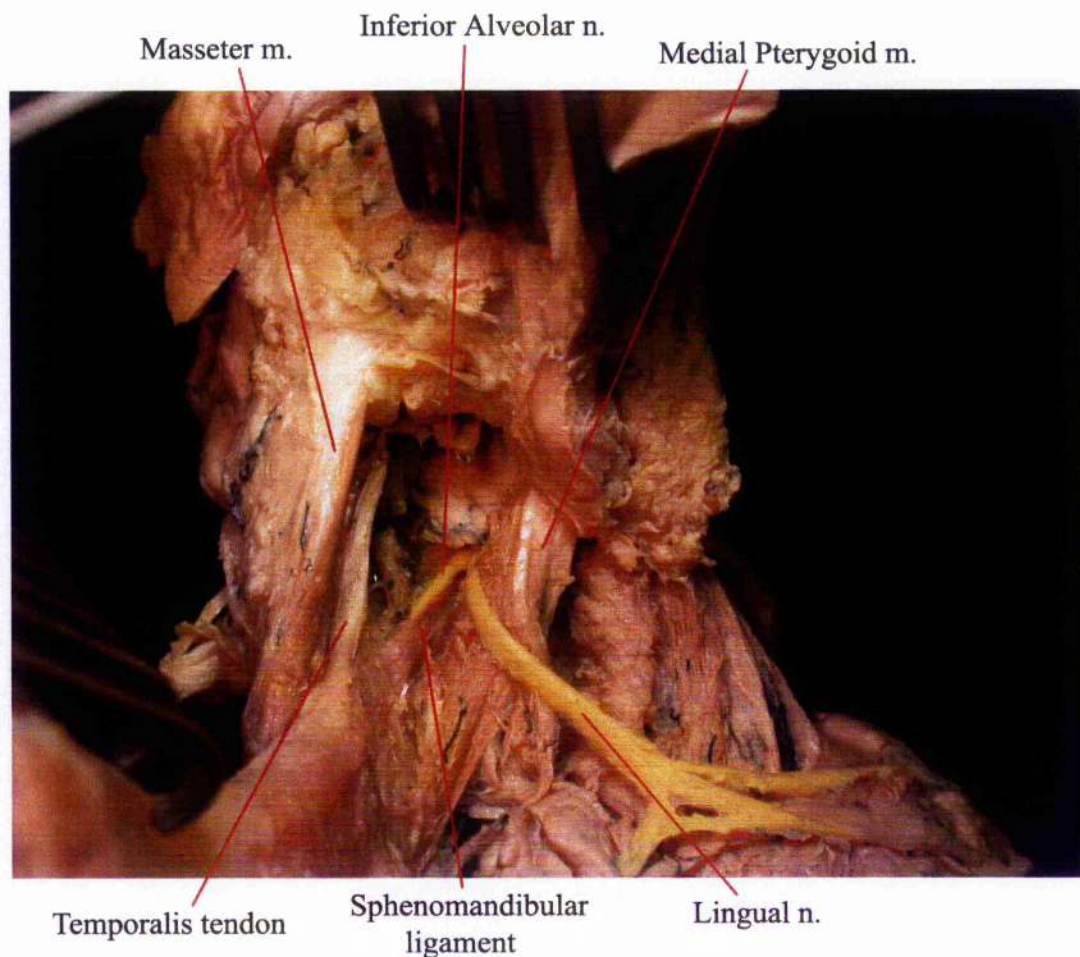


Figure 20 Gross anatomy of the Retromolar trigone.

The functional implications of damage to all of the above mentioned structures would be in terms of difficulties in speech, chewing and swallowing.

The oral stage of swallowing requires the action of the mylohyoid, styloglossus and intrinsic muscles of the tongue. Movements of the tongue are essential in deglutition. Goldie et al's investigation showed damage is likely to palatoglossus at least, thereby restricting this

movement (68). As the soft palate is often involved in tumour spread, removal inflicts upon patients the distressing sensation of food passing into the nasopharynx on swallowing. The pterygomandibular raphe links buccinator and the superior constrictor of the pharynx. Damage to it would interfere with the stability of these muscles and inhibit their function: superior constrictor in the pharyngeal stage of swallowing; buccinator is important in chewing and bolus preparation.

Motor control of speech is thought to operate via an afferent feedback control loop, whereby the sensory fibres of the oral cavity relay information back to the speech areas of the brain. According to this theory, damage to these afferent fibres during surgery would have detrimental implications for the patient's speech. Experiments have taken place in attempt to simulate such an event. Local anaesthetic was injected bilaterally along the medial surface of the mandible resulting in complete anaesthesia to touch and pain of the tongue, lower lip and surface tissues of the mandible. This was considered to be the sensory domains of the inferior alveolar and lingual nerves. Subjects were then assessed for speech errors. Speech was found to be considerably distorted (this is supported by anecdotal evidence following visits to the dentist), however, subjects were generally able to compensate their speech to retain it at intelligible level (69). This correlates with the clinical picture seen in oral cancer patients postoperatively.

A clinical study by Goldie et al., showed correlation between injuries caused at operation in the RMT compared with an objective oral function scale in terms of speech and swallowing (70). It was shown that clinical tumour size could be used to predict the extent of functional deficit that RMT cancer surgery produces.

Incisions in the RMT will cause injury to certain oral structures with likely functional consequences. Damage to medial pterygoid and palatoglossus muscles can create difficulties with swallowing and speech. Division of the lingual nerve will result in loss of sensation in

the tongue, which can also affect oral function. Such alterations may be additional to those caused by anatomical distortion resulting from tumour excision and reconstruction.

The findings of cadaver dissections pose immediate concerns for surgeons operating in RMT area. Although cancer surgery often involves sacrificing tissue, care should be taken to preserve structures vital to the patient's oral function without compromising oncological principles.

Natural History

Epidemiology

This retrospective study comprises 113 patients with squamous cell carcinoma of the RMT treated at Canniesburn Hospital, Glasgow, between 1985 and 1999. Seventy-eight (69%) were males and 35 (31%) were females. The male to female ratio for the whole group of patients was 2.2:1.

The average age of patients was 65 years (range 37-90 years). The average age of males was 63.5 years (range 37-90 years) and 66 years (range 47-88 years) for females. The age distribution of patients is shown in Figure 21.

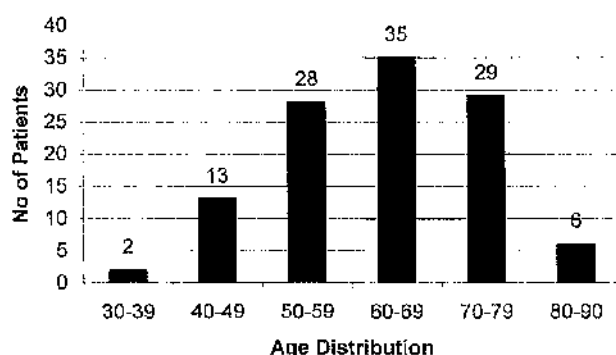


Figure 21 Age distribution of patients ($n = 113$).

Ninety-four percent were smokers (average one pack of cigarettes/day). From that percentage 20.5% were ex-smokers.

Thirty-one percent were heavy alcohol drinkers (more than 30 units per week).

Of the 113 patients, 108 had a primary untreated squamous cell carcinoma of the retromolar trigone, while the remaining 5 had a second primary tumour in this area. The majority of the cases (91 patients) were referred to the Head and Neck Clinic of Canniesburn Hospital from a consultant (Dentist, ENT surgeon, Maxillofacial surgeon) within the Trust. The rest were referred directly from their General Practitioner.

Pathology

All 113 patients had histologically proven squamous cell carcinoma of the retromolar trigone area. Twenty-six had poorly differentiated carcinoma, 5 were moderately, 3 were well differentiated and one was undifferentiated. The degree of differentiation has been included in the pathology report from 1995 onwards. The average tumour thickness was 3mm.

In 7 specimens out of 26 there was perineural invasion and in 12 out of 26 there was vascular/lymphatic invasion. Those last tumour prognostic factors were included in the pathology reports only in the last 3 years of the study.

The resected margins were clear (>5mm) in 64 cases, close (1-5mm) in 7 cases, involved in 22 cases, while the remaining 20 patients (unknown) underwent diagnostic biopsy only or were initially treated with radiotherapy.

Of the whole group 71 patients (63%) had a clinically negative neck at presentation and 42 patients (37%) had a clinically positive neck. The most commonly involved nodal group in the metastasis was level II. Eleven patients, all with positive nodes at levels I and/or II, had histologically positive nodes at levels III and IV. Only one patient with positive nodes at level I and II on the ipsilateral side, had contralateral node metastasis at level III. A total of 85 patients (75%) had a neck dissection at the time of initial treatment of the primary (51 were considered elective from a clinical point of view and 34 therapeutic). Of these 85 patients, 45 (53%) proved to have pathologically involved lymph nodes at presentation.

Results regarding the pathologically staging of the tumors are analysed in details in a following chapter

Patterns of spread

The most common sites of extension of the cancer were to the soft palate in 48% (54/113) of cases, the tonsillar pillar in 39% (44/113), the lower gum, the buccal mucosa and the floor of mouth, each in 10% (12/113) of cases. Other areas involved were the posterolateral part of tongue, the posterolateral pharyngeal wall and the maxillary sinus. Seventy-two percent (82/113) of patients had at least one adjacent area involved, while 28% (31/113) had only the retromolar trigone involved. The overall incidence of pathologically proven cancer invading bone was 23% (26/113).

Clinical Presentation and Diagnosis

Figure 22 & Figure 23 demonstrate the clinical presentation of a SCC of the RMT of two different patients presented at Canniesburn Hospital.

The commonest presenting symptom was pain (including pain in the local area, sore throat and otalgia) in 37% (42/113) of cases, followed by an intraoral mass or ulcer in 24% (27/113) and dysphagia in 16% (18/113) of cases. Trismus was the main presenting symptom in only 6 cases. Out of 3 patients complaining about a neck mass, only one had this as the only presenting symptom.



Figure 22 SCC of the left retromolar trigone.

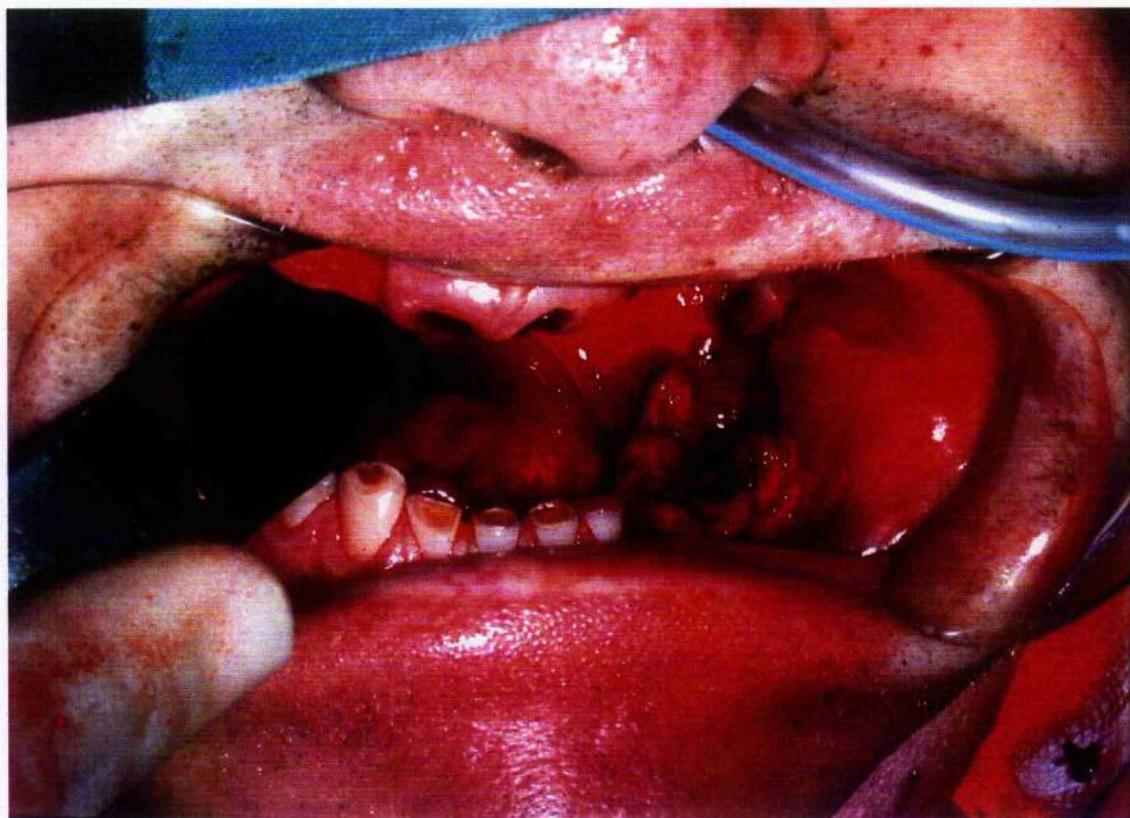


Figure 23 SCC of the left retromolar trigone.

The average duration of symptoms prior to presentation was 1 month for clinical T1 lesions ($n = 11$), 2 months for T2 lesions ($n = 47$), 3 months for T3 lesions ($n = 18$), 2 months for T4 lesions ($n = 37$) and overall 2 months ($n = 113$). There was no significant statistical correlation between length of symptoms and T stage of tumour (Kendall's tau-b (t) = 0.17, $P = 0.838$).

The average time from diagnosis till surgery was approximately 3 weeks, while the average time from first seen in our hospital till surgery was 2 weeks.

Staging

A total of 9.7% of patients were clinically staged as T1, 41.6% as T2, 16% as T3 and 32.7% as T4.

Post-surgical (pathological) staging according to UICC classification of patients after surgery performed at Canniesburn Hospital is shown in Table 10. In 23 patients the primary tumour was not staged pathologically. This included those undergoing palliation and radiotherapy only as the treatment modality.

The accuracy of clinical assessment of T stage compared to pathological staging is shown in Table 11. The primary tumour was upstaged in 15.5% of patients (14/90) and downstaged in 11% (10/90).

Table 10 Post-surgical (pathological) staging of patients according to UICC classification

		pN stage					x	Total
		N0	N1	N2a	N2b	N2c		
pT stage	pT1	13	0	0	0	0	1	14
	pT2	10	7	1	9	0	2	29
	pT3	2	2	0	7	0	0	11
	pT4	18	6	1	10	1	0	36
x		1	0	0	2	0	20	23
Total		44	15	2	28	1	23	113

Table 11 Accuracy of clinical T staging compared to pathological T staging according to UICC classification

		Clinical T stage				Total
		T1	T2	T3	T4	
pT stage	pT1	7	7	0	0	14
	pT2	1	25	2	1	29
	pT3	0	1	10	0	11
	pT4	0	7	5	24	36
x		3	7	1	12	23
Total		11	47	18	37	113

The accuracy of clinical assessment of neck nodes showed pathological upstaging of disease in 21% and downstaging in 9% (Table 12).

Table 12 Accuracy of clinical assessment of status of neck nodes

	Clinical N0	Clinical N +ve	Total
Pathological N0	36(True -ve)	8(False +ve)	44
Pathological N +ve	19(False -ve)	27(True +ve)	46
x	16	7	23
Total	71	42	113

False positive rate= $8/44 = 18\%$, Specificity= $36/44= 82\%$.

False negative rate= $19/46 = 41\%$, Sensitivity= $27/46= 59\%$.

Treatment protocol

The selection of treatment was determined in a non-randomized manner. Throughout the study period the policy at this unit was to surgically excise the primary tumour if possible (41;46). Patients with a clinically positive neck underwent a therapeutic neck dissection and most of the patients with a clinically negative neck underwent elective neck dissection, for better access to the primary tumour, reconstruction requirements or cases deemed at high risk for developing cervical metastasis. Radiotherapy was given postoperatively depending on the bulk of the tumour, depth of infiltration, closeness of resection margins and a positive lymph node in the neck.

Exceptions to this treatment protocol included patients who refused surgery, those excluded for medical reasons, recurrence following previous treatment and cases treated for palliation. The treatment protocols are detailed in Table 13.

Table 13 Initial treatment protocol of primary site

Initial treatment protocol	No. of patients	(%)
Combined (surgery and postoperative radiotherapy)	75	(66.4)
Surgery only	20	(17.8)
Radiotherapy only	8	(7)
Other (chemotherapy+/- radiotherapy+/-surgery)	8	(7)
Supportive	2	(1.8)
Total	113	100

Management of the neck

A total of 85 patients (75%) had a neck dissection at the time of initial treatment of the primary (51 were considered elective from a clinical point of view and 34 therapeutic). Neck dissections(47) were radical in 19 cases, modified radical type I in 4, type II in 2, type III in

48, selective levels I-III (supraomohyoid) in 3, selective levels I-IV (anterolateral) in 4 and 'not otherwise specified' neck dissection in 10 cases.

Reconstruction

The defects were repaired with a free radial forearm flap in 71 patients (5 were osteocutaneous flaps), with pectoralis major muscle pedicled flap in 8, with buccal flaps in 8 and with other flaps (nasolabial, temporalis muscle, deep circumflex iliac artery, lateral arm, ulnar, tongue flap) in 11 patients. In only one patient the defect was closed primarily. Figure 24-28 show in stages the excision of a SCC of the RMT and the reconstruction of the defect with a free radial forearm flap. Figure 29-35 show in stages the excision of a SCC of the RMT and the reconstruction of the defect with a nasolabial flap.

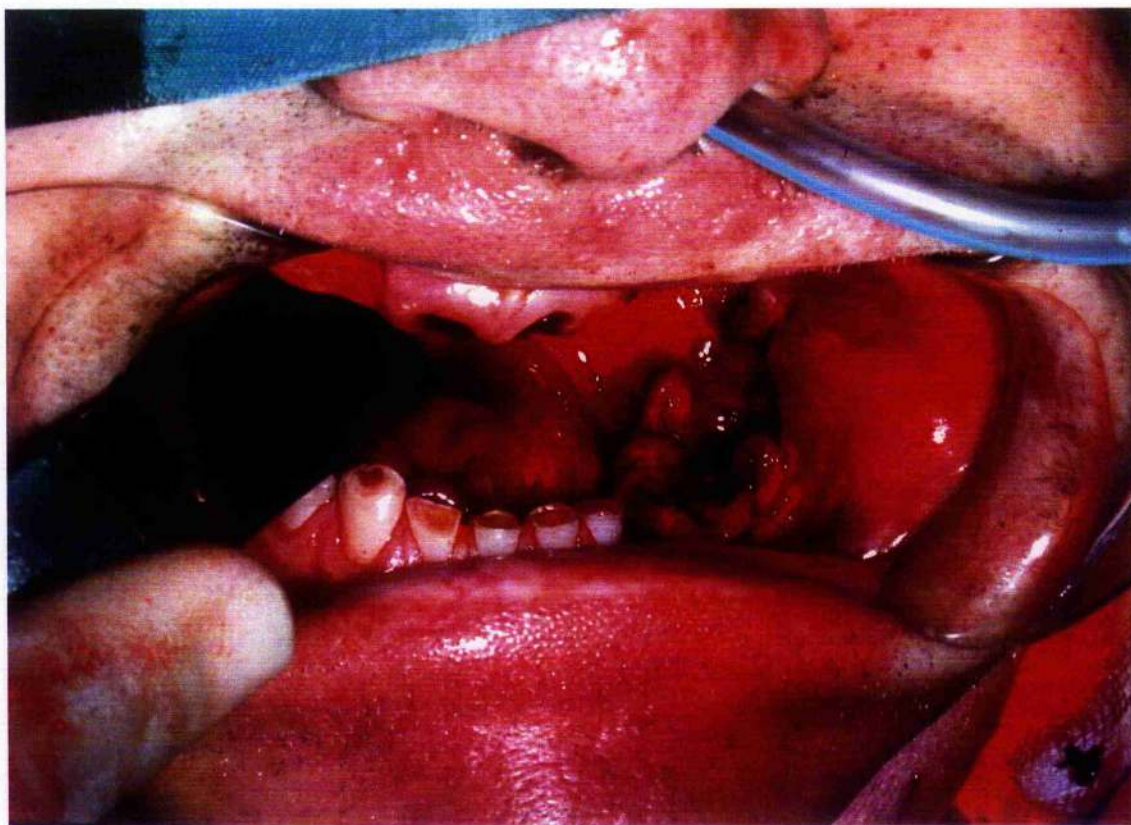


Figure 24 Squamous Cell Carcinoma of left retromolar trigone

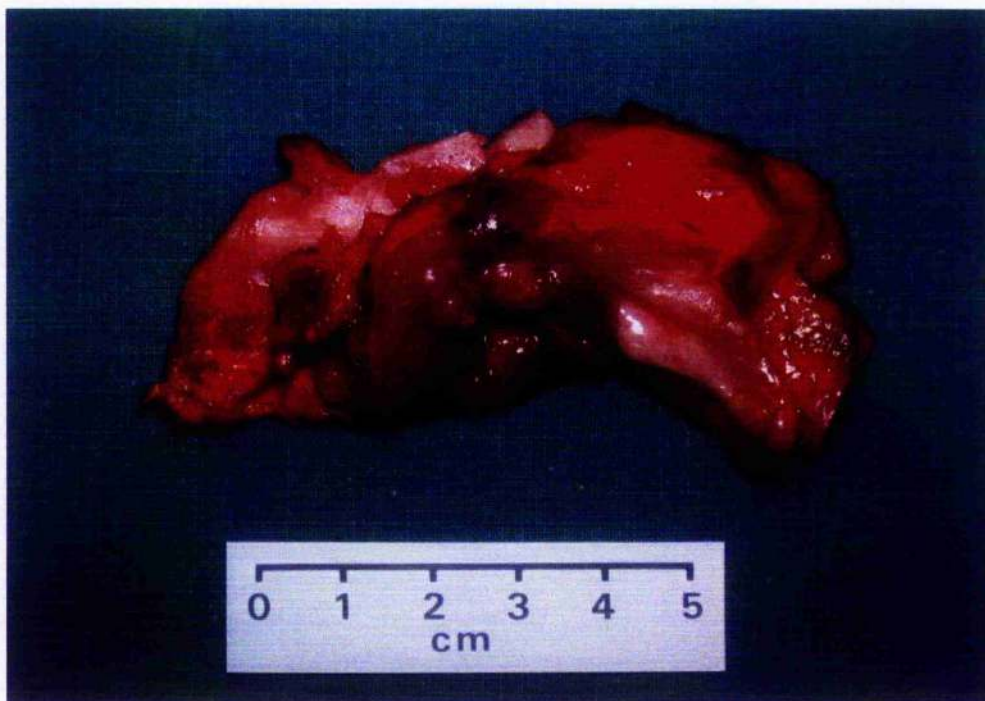


Figure 25 Tumor excised with 1cm margins

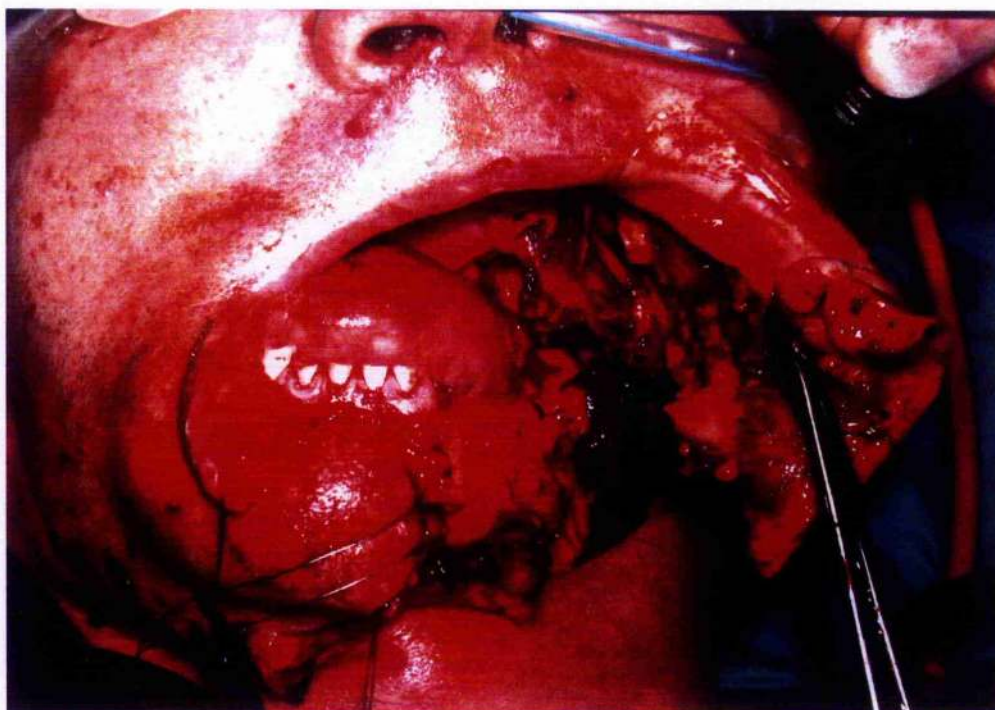


Figure 26 The defect after the excision



Figure 27 Design of free radial forearm flap

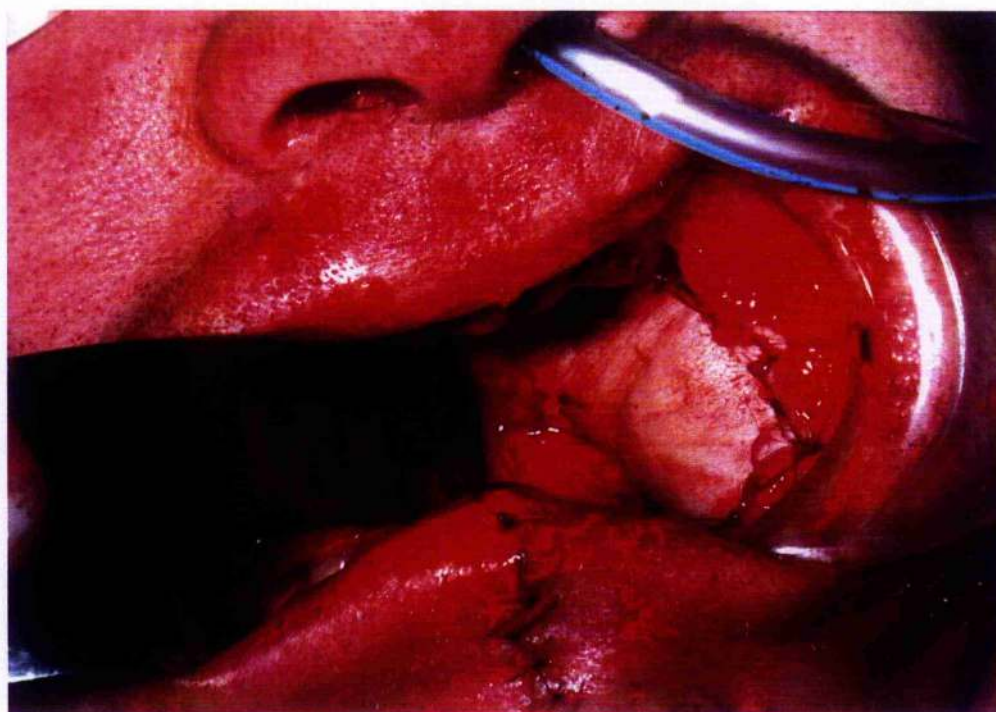


Figure 28 Insetting of the flap



Figure 29 Squamous Cell Carcinoma of left retromolar trigone



Figure 30 Tumor excised with 1cm margins and marginal mandibulectomy



Figure 31 SCC of left retromolar trigone



Figure 32 Design of a nasolabial flap



Figure 33 The nasolabial flap raised



Figure 34 Passed through a tunnel

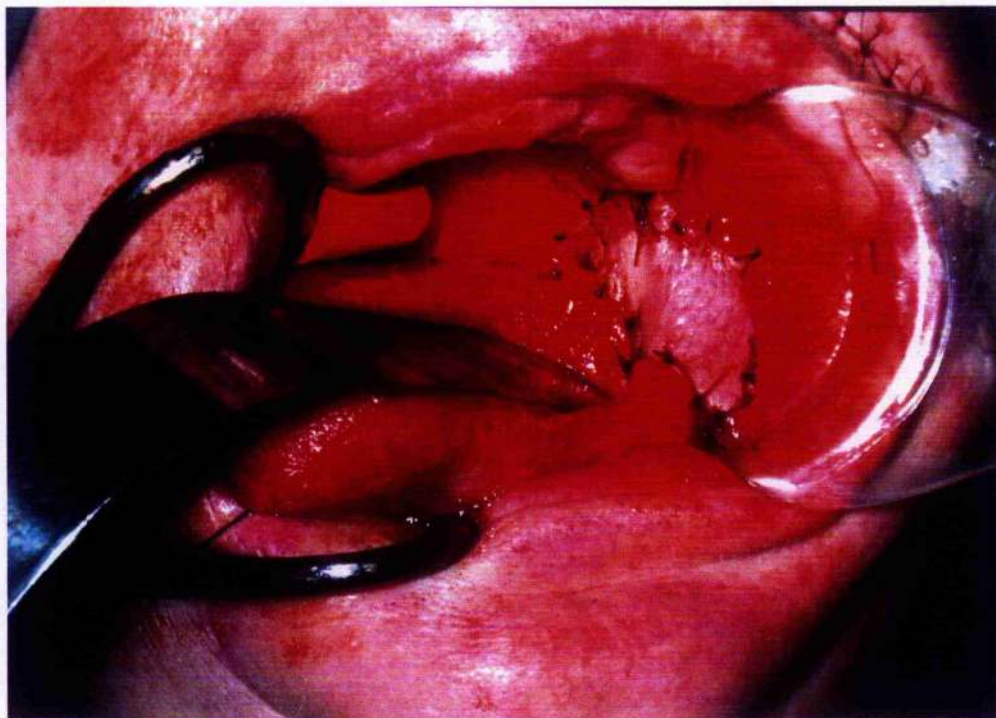


Figure 35 Nasolabial flap inset

Results of treatment

This study covers a period of 15 years from 1985 to 1999. The determinate 5-year survival rates related to pathological T stage according to UICC classification by the Kaplan-Meier method were pT1: 75%, pT2: 40%, pT3: 47%, pT4: 32% and overall 42% (logrank=7, d.f.=3, $P=0.071$) (Figure 36 and Figure 37). Clinical T stage was used for patients whose primary tumour was not initially staged pathologically ($n = 23$).

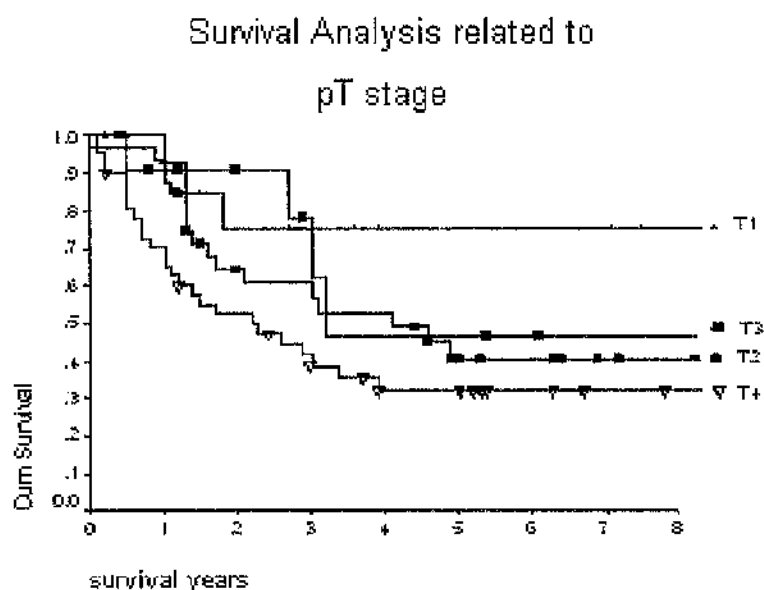


Figure 36 Corrected survival related to pT stage (UICC). Clinical T stage was used for patients whose primary tumour was not initially staged pathologically ($n = 23$).

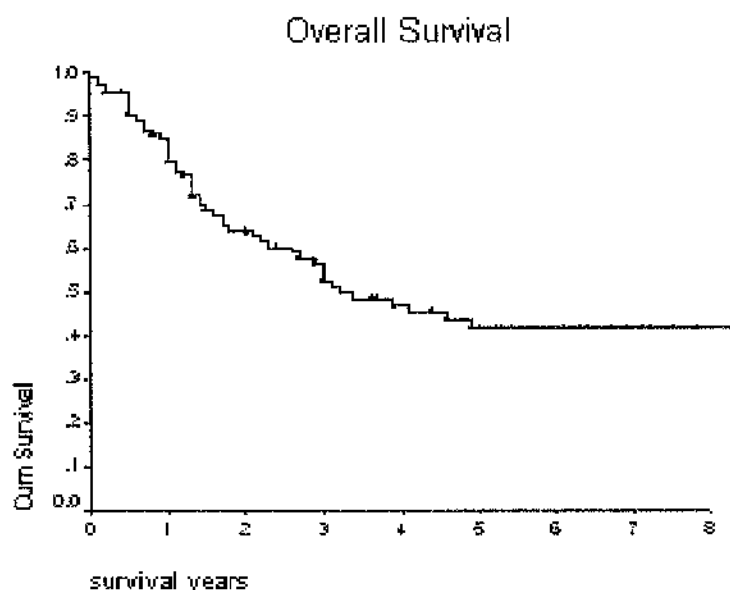


Figure 37 Corrected overall survival.

The determinate 5-year survival rates related to pathological N stage according to UICC classification by the Kaplan-Meier method were pN0: 58%, pN1: 19%, pN2/3: 28% (logrank=9, d.f.=2, $P=0.01$) (Figure 38). Clinical N stage was used for patients whose primary tumour was not initially staged pathologically ($n=23$).

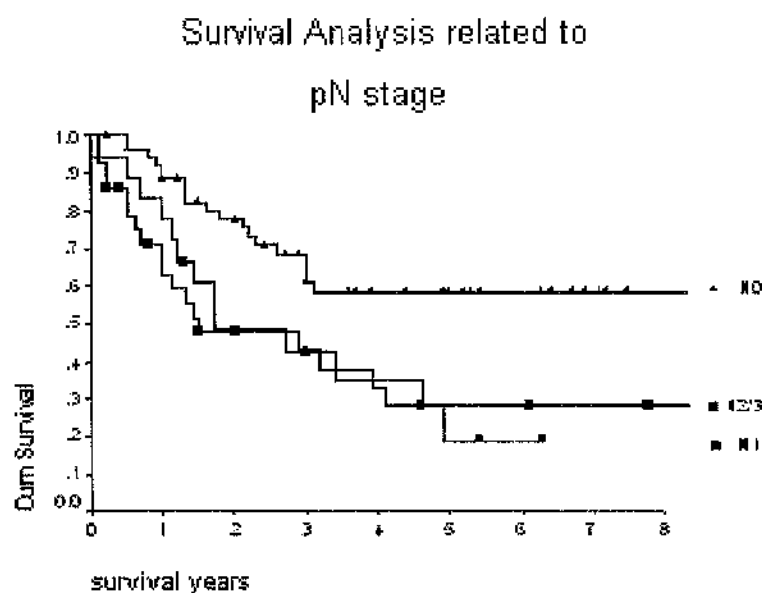


Figure 38 Corrected survival related to pN stage (UICC). Clinical N stage was used for patients whose primary tumour was not initially staged pathologically ($n=23$).

The determinate survival curves related to the status of lymph nodes found at initial neck dissection are shown in Figure 39. There was no statistically significant difference between patients with one or more than one positive lymph nodes (one vs more than one; logrank=0.42, $P=0.517$). On the other hand, patients with negative lymph nodes had a significant survival advantage over patients with positive lymph nodes (pos vs neg; logrank=9, $P = 0.027$) (Figure 39).

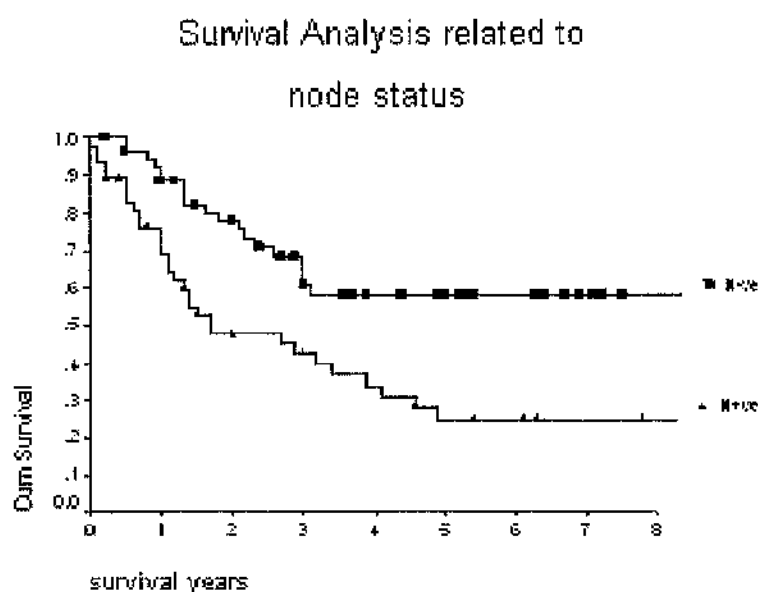


Figure 39 Corrected survival related to nodal status.

The determinate 5-year survival rates related to pathological TNM stage were stage I: 73%, stage II: 55%, stage III: 29% and stage IV 34% (logrank=5.18, d.f.=3, $P=0.158$) (Figure 40).

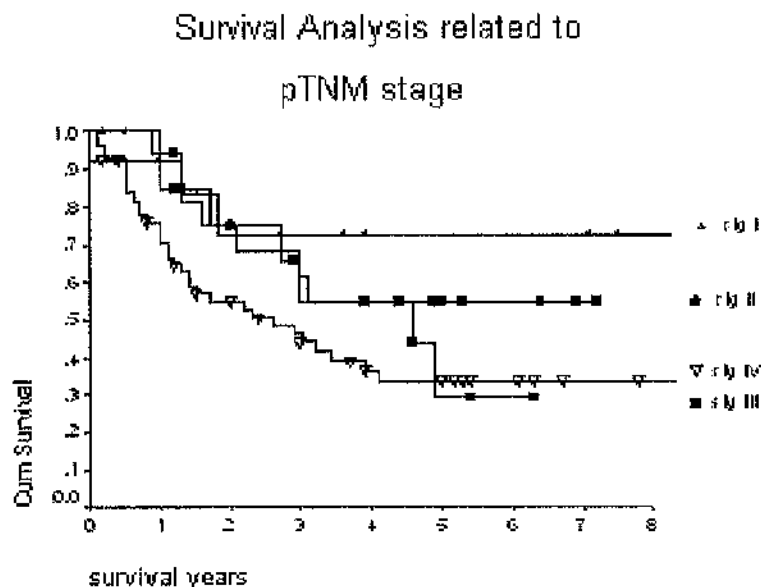


Figure 40 Corrected survival related to pTNM stage.

The determinate survival curves related to sex and age were studied and showed no statistically significant differences (male vs female logrank=0.36, $P=0.548$, and <65 years vs >65 years; logrank=0.52, $P=0.472$). The age group <65 years however did show a drop in survival rate compared to the >65 years, which was not statistically significant (Figure 41).

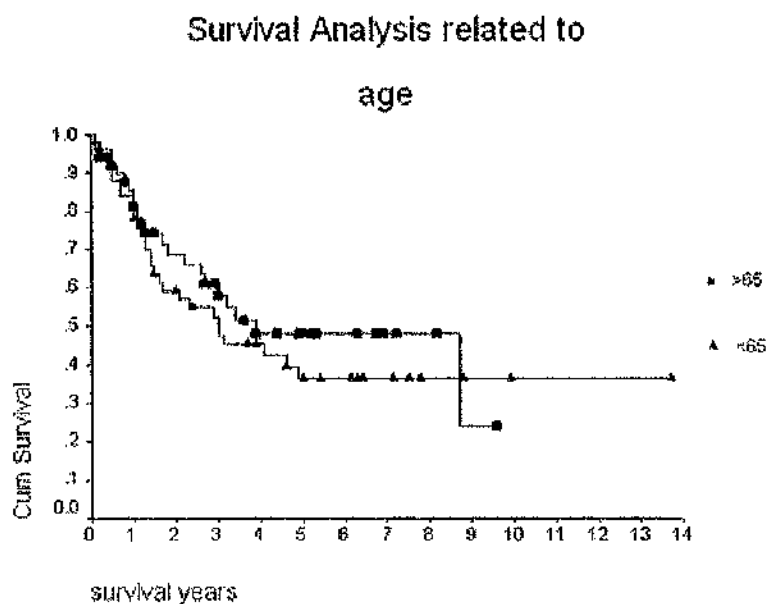


Figure 41 Corrected survival related to age.

The adequacy of resection margin for the primary tumour at the initial surgery as reported by the pathologist was: clear 64 patients, close (within 5mm of resection margin) 7 patients, involved 22 patients, while the remaining 20 patients (unknown) underwent diagnostic biopsy only or were initially treated with radiotherapy. The determinate survival curves for the three surgical groups were studied and showed statistically significant differences between them, regardless of any further treatment they may have received (clear v close; logrank = 7.13, $P = 0.007$; clear v involved; logrank = 12.95, $P = 0.0003$) (Figure 412).

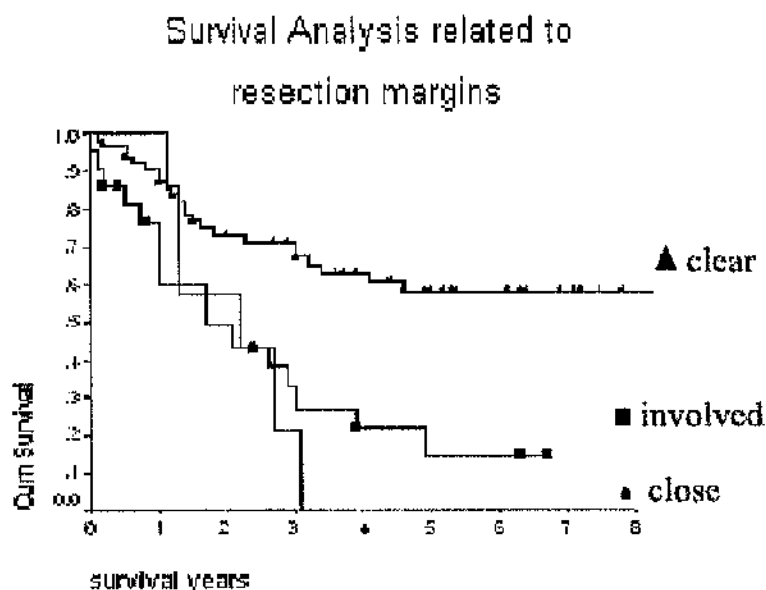


Figure 412 Corrected survival related to resection margin of primary tumour found at initial surgery.

Other confounding factors for locoregional recurrence apart from close or positive surgical margins are (71):

- Nodal involvement: Nodal involvement affects prognosis adversely. Higher numbers and more inferior levels of nodes involved are adversely related to prognosis as is extracapsular spread
- T stage: Higher T stage correlates with poorer prognosis.
- Depth of invasion: Tumour thickness of greater than 4 mm imparts a worse prognosis.
- Vascular and perineural infiltration: Perineural infiltration is a sensitive predictor of local recurrence and prognosis.
- Tumor grade: a higher grade equates to a poorer prognosis.

- Pattern of infiltration: A non-cohesive, infiltrative pattern of growth, as opposed to a cohesive pattern with broad strands and sheets of tumour, is related to a poorer outcome.
- Tumour type: Papillary and verrucous carcinomas generally have a better prognosis, whilst basaloid and spindle cell variants behave more aggressively.

The loco-regional failure and site failure considered to have been the cause of eventual demise of patients is shown in Table 14 and Table 15. In all, 38 patients (33.6%) died of disease directly related to the retromolar trigone cancer or its treatment while 29 patients (25.6%) died of unrelated conditions during the follow-up period. Systemic failure accounted for 14 patients out of 113 (12.4%). The most common distant metastases were to the lungs and liver. A total of 32% of patients in this study remain alive and well (Table 16).

Table 14 The loco-regional and systemic failure rates

Recurrence site	T1 (n=11)	T2 (n=47)	T3/4 (n=55)	Total (%) (n=113)
Lost to follow-up	2	4	4	10(8.8)
No recurrence	7	35	43	85(75)
Primary site	2	8	9	19(16.8)
Ipsilateral neck	0	0	0	0(0)
Contralateral neck	0	1	0	1(0.8)
Primary site and neck	0	1	4	5(4.4)
Second intraoral primary	1	0	0	1(0.8)
Systemic	2	2	10	14(12.4)

N.B. Some patients had more than one recurrence.

Table 15 Site failure leading to eventual demise

	T1 (n=11)	T2 (n=47)	T3/4 (n=55)	Total (%) (n=113)
Lost to follow-up	2	4	4	10(8.8)
Palliated	0	0	5	5(4.4)
Primary site	1	8	9	18(16)
Ipsilateral neck	0	0	0	0(0)
Contralateral neck	0	1	0	1(0.8)
Primary site and neck	0	1	4	5(4.4)
Second intraoral primary	0	0	0	0(0)
Systemic	2	2	10	14(12.4)
Incidental deaths	0	14	15	29(25.6)
Alive and well	6	17	13	36(31.8)

N.B. Some patients had more than one recurrence.

Table 16 Cause of death

Cause of death	<i>No. of patients (%)</i>
Disease related	38(33.6)
Incidental	29(25.6)
Lost to follow-up	10 (8.8)
Alive and well	36 (32)
Total	113 (100)

Discussion

Retromolar trigone cancer is an unusual oral cancer. Its natural history is not well known and is frequently compared with that of inferior gingival or anterior tonsillar pillar cancers (17;48-50). The natural history and patterns of treatment failure of retromolar trigone carcinoma treated in a single head and neck unit have been studied over a period of 15 years. No comparison was made between different modalities of treatment in this series because patients were not randomly assigned to a particular treatment modality. By far the majority (84%) was managed by surgical excision alone or combined with postoperative radiotherapy.

The anatomic location and the propensity for tumors of this region to invade adjacent structures (base of tongue, tonsil, palate) explains why accessibility for excision and reconstruction is difficult. Only early lesions of the RMT can be resected transorally and reconstruction can be achieved with a local advancement flap, split thickness skin graft, or healing by secondary intention. Larger tumors require increased exposure which can be achieved through a mandibulotomy. Resection of such an RMT tumour, as demonstrated from cadaveric dissection, is likely to cause injury to the lingual nerve, the inferior alveolar nerve, the submandibular duct and several muscles of the oral cavity. The functional implications would be in terms of difficulties in speech, chewing and swallowing. The efficacy of local advancement flaps and adjacent tissue transfer for reconstruction is often limited in this area either because the tissue is irradiated or because the available tissue is limited. Free tissue transfer is often the only reconstructive option that can achieve optimal functional results. Thin pliable fascial flaps that can mould into various contours, such as the radial forearm free flap, can be used to resurface the defect.

Our data analysis confirms results that have been published by others (17;48;49). Our series however has a higher incidence of women presenting with carcinoma of the retromolar trigone (male: female ratio 13:1 published in 1959 by Barbosa, 10:1 published in 1993 by Kowalski et al, 2.2:1 published by our series) (17;48), most likely explained by the increased incidence of smoking and drinking among women in recent decades. We have found no statistically significant difference in survival between the different age groups. In our series, although the group of patients younger than 65 years old had a worse outcome (5-year survival 37%) compared with the older group (5-year survival 48%), the difference failed to reach statistical significance. Interestingly enough the same result was published by Kowalski, regarding patients younger than 56 years old having a worse 5-year survival (17). Maybe this is an indication that the cancer might be more aggressive in younger patients.

We have not demonstrated any correlation between the average duration of symptoms and T stage, perhaps demonstrating the unreliability of patients' assessment of the presence of disease.

The 5-year overall survival in our series was 42%, which is higher than 20% that Byers et al (49) reported in their series of 110 patients but lower than 55.3% that Kowalski reported (17) in his series of 114 patients. Further statistical work could be carried out to evaluate the 5-year local control rates, 5-year local-regional control rates, 5-year distant metastasis-free survival rates and 5-year cause-specific survival rates. Multivariate analyses could be carried out to reveal significant predictors for locoregional and systemic failure.

The control of carcinoma of the retromolar trigone is closely related to the extent of the primary tumour and the state of the regional lymph nodes. Metastasis to regional and cervical nodes is reported in 40 to 60% of the cases (51). The frequency (41%) and distribution of lymph node metastases in this series were similar to those reported by others (17;49;52). This series has demonstrated a significant survival advantage for patients with

node negative disease (58% 5-year survival) and a significantly poorer outcome for patients with positive nodes (25% 5-year survival). In the group of patients with positive nodes, patients with only one positive node had similar survival rate compared with patients with more than one positive lymph nodes.

We have also been able to study the clinical accuracy of staging in an experienced head and neck unit. Pathology upstaged the primary tumour in 15.5% of patients (14/90) and downstaged in 11% (10/90). In the staging of neck disease, pathology upstaged 21% of clinically N0 necks and downstaged 9% of clinical N +ve disease. Kowalski et al have also reported a high incidence of false clinical diagnosis of the status of cervical lymph nodes (17).

The importance of achieving a clear resection margin at the first surgery cannot be overemphasized as survival is closely related to resection margin regardless of any subsequent therapy the patients may receive.

The natural history of squamous cell carcinoma is of loco-regional failure and our results are comparable to previous reports. Of the patients in this series 34% (38/113) died as a result of their retromolar trigone cancer or its treatment. Systemic failure accounted for 12.4% of deaths, further emphasizing the need to obtain better loco-regional control of disease.

A total of 32% of patients in this series remain alive and well, while 21% died of local or regional disease. Byers et al reported ultimate failure in the primary site in 7% and at the neck in 11% of the patients with retromolar trigone cancer (49). Kowalski found that most recurrences are local and usually seen in the first 2 years of follow-up (17). Our analysis confirms these results. In our series the average time from the date of treatment to recurrence was 45.6 weeks and 94.4% of the recurrences occurred in less than 64 weeks of follow-up. Problems with the correct staging of disease for retromolar trigone carcinoma are clearly demonstrated. This applies both to the T stage and particularly to nodal metastasis. More

accurate methods of staging the disease at the primary site and in the neck are required so that suitable treatment protocols can be adopted with the aim of improving control of disease and overall survival. This review covers patients treated from 1985 until 1999 at which time CT and MRI scanning was not used to any great extent at Canniesburn Hospital. Over the last years these techniques have become very important in assessing the tumour, assisting in the staging of the tumour and in helping the decision process regarding overall management.

The understanding of the natural history of retromolar trigone tumours as a separate entity from other intraoral squamous cell carcinomas allows us to give more accurate information about prognosis for patients presenting with squamous cell carcinoma of the retromolar trigone. It also allows us to formulate different strategies for its treatment.

Statement

My research work so far, has been presented at the winter meeting of the British Association of Plastic Surgeons (B.A.P.S.) in London, UK, 27-30 November 2002 and submitted for publication to the Journal of Plastic, Reconstructive & Aesthetic Surgery (manuscript number: JPRAS-D-07-00075).

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